Targeted therapy in antiphospholipid syndrome

Targeted therapy in antiphospholipid syndrome

Savino Sciascia

Munther A Khamashta

David P D'Cruz

[1] Graham Hughes Lupus Research Laboratory, Lupus Research Unit, The Rayne Institute, Division of Women's Health, King's College London, [2] Centro di Ricerche di Immunologia Clinica ed Immunopatologia e Documentazione su Malattie Rare (CMID), Università di Torino, Italy and [3] Louise Coote Lupus Unit, Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London, UK

Correspondence: Professor David P D'Cruz MD FRCP

Lupus Research Unit, The Rayne Institute,

St. Thomas' Hospital, London SE1 7EH, UK

Telephone: 00 (44) 207 188 3569

Fax : 00(44) 207 188 3574

E-mail: ***david.d'cruz@kcl.ac.uk***

Abstract

Purpose of review: To review novel therapeutic targets that are currently under investigation to develop safer, targeted therapies for antiphsopholipid antibody (aPL)-mediated clinical manifestations.

Recent findings: Novel therapeutic options potentially available include anti-CD20 monoclonal antibodies and new-generation anticoagulants (such as direct thrombin and anti-Xa inhibitors). Research focusing on interfering with aPL-mediated cell activation, targeting complement components and the innovative concept of blocking the pathogenic sub-population of aPL with tailored peptides are currently being explored.

Summary: Antiphospholipid syndrome is an autoimmune disease characterised by thrombosis and pregnancy morbidity occurring in patients persistently positive for aPL. Current therapeutic options remain confined to long-term anticoagulation with vitamin K antagonists. The future holds much promise with the identification of novel potential targets, many of which are currently under investigation. The challenge will be to design prospective randomized controlled clinical trials to provide the evidence necessary to support integration of these therapies into clinical practice.

Keywords: antiphospholipid antibodies, antiphospholipid syndrome, novel therapy, thrombosis, pregnancy loss

Introduction

The antiphospholipid syndrome (APS) is an autoimmune systemic disease characterised by vascular thrombosis and/or pregnancy morbidity occurring in patients persistently tested positive for antiphospholipid antibodies (aPL) [1]. Currently the only proven therapeutic option is long-term anticoagulation with vitamin K antagonists [2]. Indeed, management of APS centres on attenuating the procoagulant state whilst balancing the risks of anticoagulant therapy. However, despite the extensive use of long-term anticoagulation in the prevention and management of APS, there are ongoing concerns about efficacy and safety, including the narrow therapeutic window and numerous drug and dietary interactions. Adherence to treatment and the impact of long-term anticoagulation on daily life present many challenges for patients with APS, not least of which include so called 'non-criteria' manifestations such as cognitive dysfunction and fatigue [3]. Dietary interactions and regular, often frequent monitoring of the INR, which is inconvenient and costly, but essential to maintain the INR within the target therapeutic range are the most frequently reported patient concerns. Moreover monitoring anticoagulation with vitamin K antagonists in patients with APS can be a real challenge, as the responsiveness of reagents used in the INR test in lupus anticoagulant positive patients vary widely, potentially leading to instability of anticoagulation [4]. Possibly because of these difficulties, recurrent thromboses and obstetric complications occur despite apparently optimum therapy. There is no consensus among experts on the best management or alternative options in such difficult cases.

There is therefore a major unmet need for novel therapies that ideally can avoid the need for regular INR testing but at the same time provide assurance that APS patients will be protected from further events. The use of novel anticoagulants in APS patients with venous thrombosis is being evaluated and until the trial data is available, patients are remaining on standard Vitamin K antagonists such as warfarin. Recent progress in understanding the pathogenic mechanisms of APS have opened new horizons for targeted therapies. Anti-inflammatory and immunomodulatory pathways are currently being explored and represent promising approaches [5,6].

In this manuscript, we review novel therapeutic targets that are under investigation for the treatment of APS.

New oral anticoagulants

The new oral anticoagulants include dabigatran etexilate (Pradaxa®), a direct thrombin inhibitor, rivaroxaban (Xarelto®), apixaban (Eliquis) and edoxaban (Lixiana®), which are direct anti-Xa inhibitors. These emerging agents represent a major advance as, unlike the vitamin K antagonists, they have few reported drug interactions that could affect anticoagulant intensity and they seem not to interact with dietary foods [4, 7, 8]. All these agents have very predictable anticoagulant effects with fixed dosing regiments, making it unnecessary to routinely monitor anticoagulant intensity. Whilst this is very appealing from a patient perspective, one of the advantages of traditional vitamin K antagonists is that measuring and recording the INR ensures adherence to therapy. The lack of INR monitoring with the novel agents may introduce variability in patient adherence to therapy which could be hard to detect, an issue which is generally

under recognised with any oral therapy. APS patients are unique in that, anecdotally, many patients have a sense of their INR and feel unwell when it is below the target range, something that does not occur in other thrombotic disorders. It remains to be seen whether patients report similar symptoms with these novel agents.

The efficacy of the novel anticoagulants has been demonstrated in large phase III clinical trials [9, 10], and both rivaroxaban and dabigatran have been licensed by the European Medicines Agency for the prevention of stroke and systemic embolism in patients with atrial fibrillation [11, 12]. In a randomized, double-blind, non-inferiority trial involving patients with acute venous thromboembolism a fixed dose of oral dabigatran was found as effective and safe as warfarin, with the advantage of not requiring laboratory monitoring[13]. Rivaroxaban was superior to vitamin K antagonists in preventing a recurrent thrombotic event following 12 months post primary event warfarin administration [14]. These studies demonstrated low incidences of major bleeding, with dabigatran being at least similar if not superior to warfarin. These new agents would be expected to improve the quality of life in APS patients. However, in order to assess whether these new agents are as effective as warfarin in APS patients, we are currently conducting the RAPS (Rivaroxaban in AntiPhospholipid Syndrome, IRSCTN 68222801) trial. RAPS is a prospective randomised controlled trial of warfarin versus rivaroxaban in patients with venous thrombotic APS, with or without SLE, being maintained at a target INR of 2.5 (i.e. range 2.0–3.0)[15].

Hydroxychloroquine (HCQ) has been proposed to reduce the risk of thrombosis in clinical studies and animal models of APS [16, 17]. Its potential antithrombotic mechanisms include inhibition of platelet aggregation and adhesion [18],

cholesterol-lowering mechanisms [18] and blockade of aPL production [19]. Raden and co-workers showed that HCQ significantly reduced the binding of aPL-beta2GPI complexes to phospholipid surfaces. The drug also reduced the binding of the individual proteins to bilayers. The same study observed that HCQ also caused modest, but statistically significant, reductions of clinical antiphospholipid antibody titers [20]. HCQ was also found to reduce the disruption by aPL of the annexin A5 anticoagulant shield [21]. A beneficial effect of HCQ on primary thrombosis prevention in aPL positive patients was shown in both retrospective and prospective studies [22, 23]. Kaieser and co-workers confirmed, in a large and ethnically diverse SLE cohort including 1930 patients, that HCQ use was protective for thrombosis [23].

Recently, Albert and co-workers showed that HCQ reversed the aPL-inhibition of trophoblast IL-6 secretion and partially limited aPL-inhibition of cell migration, suggesting that some form of combination therapy that includes HCQ may be beneficial to pregnant APS patients. A randomized multicenter study has been initiated to address the prophylactic role of HCQ against thrombosis in patients with aPL [24].

Statins are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase. They have been shown to have additional anti-inflammatory, immunoregulatory and anti-thrombotic effects in vitro and in vivo [25, 26]. Their efficacy in primary and secondary prevention of cardiovascular events [27, 28] and venous thrombosis [29] has been demonstrated in the general population. Statins have been shown to decrease aPL-induced endothelial cell activation via inhibition of the expression of adhesion molecules and IL-6 and by reversal of tissue factor (TF) upregulation [30-33]. Statins also

have a variety of direct effects on gene expression and on the function of cells of both the innate and adaptive immune systems [34]. By altering isoprenylation, which in turn induces the inhibition of the small GTP-binding proteins Rho, Ras, and Rac, statins are able to decrease oxidative stress and inflammation, inhibit the thrombogenic response, and exert beneficial effects on the immune system [35]. In APS, statins have been demonstrated to interfere with monocyte, lymphocyte, and endothelial cell function, all of which may contribute to thrombosis prevention in aPL positive patients [31, 36, 37]. Preliminary results of an ongoing Phase 2 clinical trial investigating the levels of proinflammatory/prothrombotic biomarkers in aPL patients, reported a significant decrease in vascular endothelial growth factor, soluble TF and TNFα titres after 30 day's therapy with fluvastatin (40mg/daily) [38, 39]. Randomized controlled trials are needed to confirm these promising preliminary results supporting the effectiveness of statins in the prevention of thrombosis in aPL-positive patients. The major difficulty with primary prevention trials of this nature is the very large sample size needed to provide a definitive answer, and this is challenging in a condition like APS. In vitro evidence for the use of pravastatin in pregnancy are still not conclusive and its role in preventing pregnancy complications in patients positive for aPL is still debated [40]. The in vivo condition may be more complex, and the effectiveness of pravastatin in the prevention of aPL-associated pregnancy complications in humans remains under investigation.

Rituximab (RTX), is an anti-CD20 monoclonal antibody that induces rapid and almost complete depletion of CD20+ B cell populations. Originally approved for the treatment of B cell lymphomas, RTX has successfully been used in the

treatment of systemic autoimmune diseases, including systemic lupus erythematosus (SLE), ANCA associated vasculitis and rheumatoid arthritis. In contrast to rheumatoid arthritis and ANCA vasculitis however, two large randomised controlled trials of RTX failed to meet their primary end-points in SLE. Despite these results, RTX continues to be widely used 'off-label' for treatment resistant SLE. RTX use has also been reported in APS, mainly in severe cases with thrombocytopenia or autoimmune haemolytic anemia [41] and in APS patients resistant to standard therapy [42, 43]. Erre and co-workers described 12 patients with primary and SLE-associated APS who were treated with RTX [42]. RTX has also been shown to be an effective therapeutic option for life-threatening Catastrophic APS in a small number of patients [44]. B cells are likely to play a central role in the generation of the aPL-induced clinical manifestations of the disease, so could constitute a therapeutic target in APS. Anecdotally, its use has also been associated with a downregulation of aPL titers [45] and with a reduced rate of recurrent thrombosis in APS patients followed for 10–36 months post-RTX [43].

Very recently, a pilot open-label phase II trial of RTX for non-criteria manifestations of APS (such as thrombocytopenia, skin ulcers, nephropathy, and cognitive dysfunction) concluded that RTX may represent a safe option in the therapeutic arsenal for APS, However, it has been reported to be effective in controlling some but not all non-criteria manifestations of APS [46].

TF inhibition. The upregulation of TF in both immune cells, especially monocytes and the vascular endothelium seems to play a key role in the pathogenetic mechanism for aPL-induced thrombosis [47]. Inhibition of TF and associated pathways by which aPL induce TF expression may represent

potential therapeutic targets in APS. Currently, some agents have been suggested to induce in vitro TF inhibition. These include ACE inhibitors, pentoxifylline, an adenosine uptake inhibitor (dilazep), and ss-deoxyribonucleic acid derivatives (e.g, defibrotide) [48]. Novel pharmacologic strategies aiming to inhibit TF upregualtion have also been developed, mainly in cardiovascular disease. Several potential mechanisms have been targeted, including TF synthesis inhibition, TF blockade using anti-TF antibodies, or recombinant TF pathway inhibitors [49]. In an open-label trial in patients with stable coronary artery disease, Sunol-cH36, a chimeric monoclonal anti–TF antibody exhibited dose-dependent anticoagulant effects inhibiting thrombin formation [50]. The clinical applications of such strategies in APS need to be tested in well-designed clinical trials.

Nuclear factor-kB and P38 mitogen-activated kinase inhibitors: The nuclear factor-kB (NF-kB) and the p38 MAPK pathways are the major intracellular mechanisms involved in the aPL-induced activation of platelets, endothelial cells and monocytes. In vitro, NF-KB inhibition was associated with a reduction of proinflammatory/prothrombotic biomarkers, including chemokines (CX3CL1 and CCL5) and cytokines (IL-1 and TNFα) [51]. In vitro reduction of expression of TF was also observed when blocking NF-KB [51]. SB 203580 is an inhibitor of p38α and p38β which suppresses downstream activation of MAPKAP kinase-2 and heat shock protein 27. It has been shown to act at low concentration as a specific p38 MAPK inhibitor, able to significantly reduce the thrombus size and the TF activity in carotid arteries in a mouse model [52]. In a Phase I study, 24 healthy subjects were exposed to an intravenous dose of LPS preceded 3 hours earlier by administration of BIRB 796 BS (another specific p38 MAPK inhibitor),

providing preliminary observations of inhibition of coagulation, fibrinolysis and endothelial cell activation [53]. Two randomized, double-blind, placebo-controlled clinical trials investigated the safety, tolerability and efficacy of studies of VX-702, another p38 MAPK inhibitor, in active, moderate-to-severe RA patients [54]. Inhibition of NF-kB or p38 MAPK pathway might represent a new targeted treatment approach in autoimmune diseases. However, its role in APS treatment needs further investigation.

Complement inhibition. The potential role of complement in the pathogenesis of APS is currently receiving a great deal of attention. There is increasing evidence linking the coagulation and complement cascades, including the findings that human C5 incubated with thrombin generated C5a, and that C5a can trigger the expression of TF [55, 56]. Girardi et al found that C5a-C5aR interaction and neutrophils are important mediators of fetal damage in APS. Treatment with heparin, the standard therapy for pregnant patients with aPL, was observed to prevent complement activation and protected mice from pregnancy complications induced by aPL (reviewed in [57]). Mice deficient in complement components C3 and C5 were resistant to enhanced thrombosis and endothelial cell activation induced by aPL. In addition, inhibition of C5 activation by anti-C5 monoclonal antibodies has been proposed to reduce aPL-mediated prothrombotic status [58]. In a mouse-model of APS, a C5a receptor antagonist was observed to induce a reduction on aPL-mediated cellular effects, including TF expression [59]. The effective use of eculizumab, a humanised monoclonal IgG2/4κ antibody that binds the complement protein C5, preventing cleavage into C5a and C5 has been reported in severe cases of APS, such as the catastrophic variant of the syndrome [60-62]. These findings

emphasize the importance of developing and testing complement inhibition therapies in patients with APS. The PROMISSE Study (Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus) [63] is currently evaluating biomarkers that predict pregnancy morbidity and will potentially stimulate interventional trials of complement inhibition in patients at risk of aPL antibody-associated clinical manifestations [64].

Blocking of aPL/β2GPI receptors on target cells. The interaction of aPL with several cell surface receptors, including annexin A2 and toll-like receptor 4 (endothelial and monocytes), lipoprotein receptor-related protein family (platelets), and C5a receptor (neutrophils) has been investigated as potential targets to prevent aPL-induced thrombosis. Evidence indicates that annexin A2, a receptor for tissue plasminogen activator and plasminogen, binds beta$_2$GPI on target cells. Interestingly, an anti-A2 monoclonal antibody significantly decreased aPL-induced expression of thrombophilic molecules on cultured endothelial cells, indicating that blocking A2 might reduce the pathogenic effects of aPL in inducing thrombosis [65, 66]. Pierangeli and co-workers investigated the role of TIFI, a 20 amino acid synthetic peptide that shares similarity with the domain V of β_2GPI in APS. They observed the ability of TIFI to reduce aPL-mediated thrombosis in mice by competing with β2GPI and preventing its binding to target cells [67]. Inhibition of aPL binding to the receptor proteins on target cells might be important in designing new modalities for the treatment of thrombosis in APS focusing on immunomodulatory option.

Several independent groups have demonstrated that polyclonal IgGs derived from the patients with APS bind domain I (DI) of β2GPI [68-70]. Therefore, anti-

DI antibodies are likely to represent an important subpopulation of pathogenic anti-β2GPI antibodies. Theoretically, molecules that inhibit binding of these aPLs to native DI may be useful as therapeutic agents in patients with APS. This hypothesis has been proposed and preliminary results showed that a recombinant D1 molecule, and a recombinant mutant D1 with enhanced aPL binding properties, may be used as an inhibitor of aPL binding and thus inhibit aPL-induced pathogenicity [71].

Intravenous immunoglobulins (IVIG). The use of IVIG in obstetric APS refractory to standard treatment has currently failed to be implemented widely due to its lack of evidence of efficacy, expense and supply shortages [72]. Studies have failed to observe statistically significant improvements in obstetric and neonatal outcomes with the use of IVIG in combination with aspirin and low molecular weight heparin (LMWH), when compared to aspirin and LMWH only regimens [73,74]. Consequently, IVIG is often reserved for patients that are refractory to LMWH or when additional indications such as autoimmune thrombocytopenia are present.

More recently, two studies [75,76] showed the efficacy of IVIG in addition to conventional therapy, in primary and secondary APS patients, in preventing the occurrence of further thromboembolic events. However, further clinical studies on a larger group of patients are necessary to fully understand the mechanisms of action and the optimal doses of IVIG in thrombotic APS.

Autologous hematopoietic stem cell transplantation. Autologous hematopoietic stem cell transplantation (HSCT) is currently being evaluated as a treatment for autoimmune diseases [77]. In 2005, Burt and co-workers suggested that autologous HSCT might be performed safely in patients with APS and appeared

to be effective therapy for eliminating aPL and preventing thrombotic complications in patients with SLE [78]. However, few cases of HSCT in APS have been reported [79, 80] and long term follow-up data are required before this option could be considered a potential therapeutic approach for the syndrome.

Conclusion

In the long-term management of APS patients, controlled studies with vitamin k antagonist alternatives, such as the new anticoagulant agents (oral direct and indirect thrombin inhibitors) are essential. Newer therapeutic agents targeting pathways involved in the development of aPL-mediated clinical manifestations are under investigation. However, the multifactorial mechanisms underlying thrombosis and pregnancy morbidity in APS are still not fully understood and this might limit the development of new targeted therapies for APS. Potentially, the current 'antithrombotic' approach to APS patients will be replaced in the future by an 'immunomodulatory' approach as our understanding of the mechanisms of aPL-mediated clinical manifestations improves.

Conflict of Interest:

None

Take home message:

- current therapeutic options for the treatment of the antiphospholipid syndrome (APS) remain confined to long-term anticoagulation with vitamin K antagonists.
- Novel therapeutic options potentially available include anti-CD20 monoclonal antibodies and new-generation anticoagulants (such as direct thrombin inhibitor and direct anti-Xa inhibitors), statins and HCQ. Strategies aimed at cellular aPL/β2GPI targets including domain 1 of anti- β2GPI are promising.
- The challenge will be to undertake carefully designed prospective multi-centre trials to produce the level of evidence required to support the inclusion of new therapies into clinical practice.

•• An important study describing independent predictors of thrombosis for aPL-positive patients including male sex, LA, and persistently positive aCL.

References

1. 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). Journal of thrombosis and haemostasis. J Thromb Haemost, 2006; 4; 2; 295-306.

2. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. The New England journal of medicine. 1995; 332;15;993-997.

3. Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA. Antiphospholipid syndrome. Lancet. 2010; 376;9751;1498-1509.

4. Arachchillage DJ, Cohen H. Use of New Oral Anticoagulants in Antiphospholipid Syndrome. Current rheumatology reports. 2013;15;6;331

5. Pericleous C, Ioannou Y. New therapeutic targets for the antiphospholipid syndrome. Expert Opin Ther Tar. 2010;14;12;1291-1299.

6. Pierangeli SS, Erkan D. Antiphospholipid syndrome treatment beyond anticoagulation: are we there yet? Lupus. 2010; 19; 4; 475-485.

7. Pradaxa 150 mg hard capsules: summary of product characteristics (SPC), EU. Boehringer Ingelheim International GmBH, 21/09/2012. Available from: www.emc.medicines.org.uk.

8. Xarelto 10 mg film-coated tablets. Summary of product characteristics (SPC), EU. Bayer HealthCare AG. Date of first authorisation/renewal of

authorisation: 30/09/08. Date of revision 12/2011. Available from: www.emc.medicines.org.uk.

9. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2009; 361;12;1139-1151.

10. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. The New England journal of medicine. 2011; 365;10;883-891.

11. Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency 26/07/2012 Pradaxa -EMEA/H/C/000829 -II/0032.

12. Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency. 09/12/2011 Xarelto -EMEA/H/C/000944 -X/0010.

13. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. The New England journal of medicine. 2009; 361;24;2342-2352.

14. Buller HR, Lensing AW, Prins MH, Agnelli G, Cohen A, Gallus AS, et al. A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study. Blood. 2008; 112;6;2242-2247.

15. Giles I, Khamashta M, D'Cruz D, Cohen H. A new dawn of anticoagulation for patients with antiphospholipid syndrome? Lupus. 2012; 21;12;1263-1265.

16. Edwards MH, Pierangeli S, Liu X, Barker JH, Anderson G, Harris EN. Hydroxychloroquine reverses thrombogenic properties of antiphospholipid antibodies in mice. Circulation. 1997; 96;12;4380-4384.

17. Fangtham M, Petri M. 2013 update: Hopkins lupus cohort. Current rheumatology reports. 2013; 15;9;360.

18. Wallace DJ, Linker-Israeli M, Metzger AL, Stecher VJ. The relevance of antimalarial therapy with regard to thrombosis, hypercholesterolemia and cytokines in SLE. Lupus. 1993; 2 Suppl 1:S13-15.

19. Ho KT, Ahn CW, Alarcon GS, Baethge BA, Tan FK, Roseman J, et al. Systemic lupus erythematosus in a multiethnic cohort (LUMINA): XXVIII. Factors predictive of thrombotic events. Rheumatology (Oxford). 2005; 44;10;1303-1307.

20. Rand JH, Wu XX, Quinn AS, Chen PP, Hathcock JJ, Taatjes DJ. Hydroxychloroquine directly reduces the binding of antiphospholipid antibody-beta2-glycoprotein I complexes to phospholipid bilayers. Blood. 2008; 112;5;1687-1695.

21. Rand JH, Wu XX, Quinn AS, Ashton AW, Chen PP, Hathcock JJ, et al. Hydroxychloroquine protects the annexin A5 anticoagulant shield from disruption by antiphospholipid antibodies: evidence for a novel effect for an old antimalarial drug. Blood. 2010; 115;11;2292-2299.

22. Tektonidou MG, Laskari K, Panagiotakos DB, Moutsopoulos HM. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. Arthritis and rheumatism. 2009; 61;1;29-36.

23. Kaiser R, Cleveland CM, Criswell LA. Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multi-ethnic cohort. Annals of the rheumatic diseases. 2009;68;2;238-241.

24. Hydroxychloroquine for the First Thrombosis Prevention in Antiphospholipid Antibody Positive Patients, IRSCTN NCT01784523.

25. Ferrara DE, Liu X, Espinola RG, Meroni PL, Abukhalaf I, Harris EN, et al. Inhibition of the thrombogenic and inflammatory properties of antiphospholipid antibodies by fluvastatin in an in vivo animal model. Arthritis and rheumatism. 2003; 48;11;3272-3279.

26. Meroni PL, Raschi E, Testoni C, Tincani A, Balestrieri G, Molteni R, et al. Statins prevent endothelial cell activation induced by antiphospholipid (anti-beta2-glycoprotein I) antibodies: effect on the proadhesive and proinflammatory phenotype. Arthritis and rheumatism. 2001; 44;12;2870-2878.

27. Merwick A, Albers GW, Arsava EM, Ay H, Calvet D, Coutts SB, et al. Reduction in early stroke risk in carotid stenosis with transient ischemic attack associated with statin treatment. Stroke; a journal of cerebral circulation. 2013 Oct; 44;10;2814-2820.

28. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ. 2010; 340:c2197.

29. Glynn RJ, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. The New England journal of medicine. 2009; 360;18;1851-1861.

30. Pierangeli SS, Ferrara DE. More on: fluvastatin inhibits up-regulation of tissue factor expression by antiphospholipid antibodies on endothelial cells. Journal of thrombosis and haemostasis : JTH. 2005; 3;5;1112-1113.

31. Ferrara DE, Swerlick R, Casper K, Meroni PL, Vega-Ostertag ME, Harris EN, et al. Fluvastatin inhibits up-regulation of tissue factor expression by antiphospholipid antibodies on endothelial cells. Journal of thrombosis and haemostasis. J Thromb Haemost. 2004; 2;9;1558-1563.

32. Girardi G. Pravastatin prevents miscarriages in antiphospholipid antibody-treated mice. Journal of reproductive immunology. 2009; 82; 2;126-131.

33. Lopez-Pedrera C, Ruiz-Limon P, Aguirre MA, Barbarroja N, Perez-Sanchez C, Buendia P, et al. Global effects of fluvastatin on the prothrombotic status of patients with antiphospholipid syndrome. Annals of the rheumatic diseases. 2011; 70;4;675-682.

34. Sivapalaratnam S, Basart H, Watkins NA, Maiwald S, Rendon A, Krishnan U, et al. Monocyte gene expression signature of patients with early onset coronary artery disease. PloS one. 2012; 7;2;e32166.

35. Liao JK, Laufs U. Pleiotropic effects of statins. Annual review of pharmacology and toxicology. 2005; 45:89-118.

36. Lopez-Pedrera C, Ruiz-Limon P, Aguirre MA, Rodriguez-Ariza A, Cuadrado MJ. Potential use of statins in the treatment of antiphospholipid syndrome. Current rheumatology reports. 2012; 14;1;87-94.

• Good review of the potential role for statins in the prevention of APS thrombosis

37. Lockshin MD, Pierangeli SS. Statins for the treatment of obstetric complications in antiphospholipid syndrome? Journal of reproductive immunology. 2010; 84;2;206; author reply 206-207.

38. ClinicalTrials.gov Identifier: NCT00674297.

39. Jajoria P, Murthy V, Papalardo E, Romay-Penabad Z, Gleason C, Pierangeli SS. Statins for the treatment of antiphospholipid syndrome? Annals of the New York Academy of Sciences. 2009; 1173;736-745.

40. Odiari EA, Mulla MJ, Sfakianaki AK, Paidas MJ, Stanwood NL, Gariepy A, et al. Pravastatin does not prevent antiphospholipid antibody-mediated changes in human first trimester trophoblast function. Hum Reprod. 2012; 27;10;2933-2940.

41. Barcellini W, Zanella A. Rituximab therapy for autoimmune haematological diseases. European journal of internal medicine. 2011; 22;3;220-229.

42. Erre GL, Pardini S, Faedda R, Passiu G. Effect of rituximab on clinical and laboratory features of antiphospholipid syndrome: a case report and a review of literature. Lupus. 2008; 17;1;50-55.

43. Bakshi J, Stevens R. Rituximab therapy for recurrent thromboembolic disease in antiphospholipid syndrome. Lupus. 2013; 22;8;865-867.

44. Berman H, Rodriguez-Pinto I, Cervera R, Morel N, Costedoat-Chalumeau N, Erkan D, et al. Rituximab use in the catastrophic antiphospholipid syndrome: Descriptive analysis of the CAPS registry patients receiving rituximab. Autoimmunity reviews. 2013 ; 12;11;1085-1090.

45. Sciascia S, Naretto C, Rossi D, Bazzan M, Roccatello D. Treatment-induced downregulation of antiphospholipid antibodies: effect of rituximab alone

on clinical and laboratory features of antiphospholipid syndrome. Lupus. 2011; 20;10;1106-1108.

46. Erkan D, Vega J, Ramon G, Kozora E, Lockshin MD. A pilot open-label phase II trial of rituximab for non-criteria manifestations of antiphospholipid syndrome. Arthritis and rheumatism. 2013; 65;2;464-471.

•• An important pilot study of rituximab in APS

47. Boles J, Mackman N. Role of tissue factor in thrombosis in antiphospholipid antibody syndrome. Lupus. 2010; 19;4;370-378.

48. Zhou H, Wolberg AS, Roubey RA. Characterization of monocyte tissue factor activity induced by IgG antiphospholipid antibodies and inhibition by dilazep. Blood. 2004; 104;8;2353-2358.

49. Holy EW, Tanner FC. Tissue factor in cardiovascular disease pathophysiology and pharmacological intervention. Adv Pharmacol. 2010; 59:259-292.

50. Morrow DA, Murphy SA, McCabe CH, Mackman N, Wong HC, Antman EM. Potent inhibition of thrombin with a monoclonal antibody against tissue factor (Sunol-cH36): results of the PROXIMATE-TIMI 27 trial. European heart journal. 2005; 26;7;682-688.

51. Kubota T, Fukuya Y, Hashimoto R, Kanda T, Suzuki H, Okamura Y, et al. Possible involvement of chemokine-induced platelet activation in thrombophilic diathesis of antiphospholipid syndrome. Annals of the New York Academy of Sciences. 2009; 1173:137-145.

52. Vega-Ostertag ME, Ferrara DE, Romay-Penabad Z, Liu X, Taylor WR, Colden-Stanfield M, Pierangeli SS. Role of p38 mitogen-activated protein

kinase in antiphospholipid antibody-mediated thrombosis and endothelial cell activation. J Thromb Haemost. 2007;5;9;1828-34.

53. Branger J, van den Blink B, Weijer S, Gupta A, van Deventer SJ, Hack CE, et al. Inhibition of coagulation, fibrinolysis, and endothelial cell activation by a p38 mitogen-activated protein kinase inhibitor during human endotoxemia. Blood. 2003; 101;11;4446-4448.

54. Damjanov N, Kauffman RS, Spencer-Green GT. Efficacy, pharmacodynamics, and safety of VX-702, a novel p38 MAPK inhibitor, in rheumatoid arthritis: results of two randomized, double-blind, placebo-controlled clinical studies. Arthritis and rheumatism. 2009; 60;5;1232-1241.

55. Huber-Lang M, Sarma JV, Zetoune FS, Rittirsch D, Neff TA, McGuire SR, et al. Generation of C5a in the absence of C3: a new complement activation pathway. Nature medicine. 2006; 12;6;682-687.

56. Redecha P, Tilley R, Tencati M, Salmon JE, Kirchhofer D, Mackman N, et al. Tissue factor: a link between C5a and neutrophil activation in antiphospholipid antibody induced fetal injury. Blood. 2007; 110;7;2423-2431.

57. Girardi G. Guilty as charged: all available evidence implicates complement's role in fetal demise. Am J Reprod Immunol. 2008; 59;3;183-192.

58. Pierangeli SS, Vega-Ostertag M, Liu X, Girardi G. Complement activation: a novel pathogenic mechanism in the antiphospholipid syndrome. Annals of the New York Academy of Sciences. 2005; 1051:413-420.

59. Carrera-Marin AL R-PZ, Qu HC, et al. A C5a receptor antagonist ameliorates in vivo effects of antiphospholipidantibodies. Arthritis and rheumatism. 2009; 60:s767

60. Lonze BE, Zachary AA, Magro CM, Desai NM, Orandi BJ, Dagher NN, et al. Eculizumab Prevents Recurrent Antiphospholipid Antibody Syndrome and Enables Successful Renal Transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2014 Jan 8. [Epub ahead of print]

61. Espinosa G, Berman H, Cervera R. Management of refractory cases of catastrophic antiphospholipid syndrome. Autoimmunity reviews. 2011; 10;11;664-668.

62. Lonze BE, Singer AL, Montgomery RA. Eculizumab and renal transplantation in a patient with CAPS. The New England journal of medicine. 2010; 362;18;1744-1745.

63. NCT00198068. Cgi.

64. Salmon JE, Girardi G. Theodore E. Woodward Award: antiphospholipid syndrome revisited: a disorder initiated by inflammation. Transactions of the American Clinical and Climatological Association. 2007; 118; 99-114.

65. Romay-Penabad Z, Montiel-Manzano MG, Shilagard T, Papalardo E, Vargas G, Deora AB, et al. Annexin A2 is involved in antiphospholipid antibody-mediated pathogenic effects in vitro and in vivo. Blood. 2009; 114;14;3074-3083.

66. Zhang J, McCrae KR. Annexin A2 mediates endothelial cell activation by antiphospholipid/anti-beta2 glycoprotein I antibodies. Blood. 2005; 105;5;1964-1969.

67. Ostertag MV, Liu X, Henderson V, Pierangeli SS. A peptide that mimics the Vth region of beta-2-glycoprotein I reverses antiphospholipid-mediated thrombosis in mice. Lupus. 2006; 15;6;358-365.

68. Ioannou Y, Pericleous C, Giles I, Latchman DS, Isenberg DA, Rahman A. Binding of antiphospholipid antibodies to discontinuous epitopes on domain I of human beta(2)-glycoprotein I: Mutation studies including residues R39 to R43. Arthritis Rheum 2007; 56; 280–90

69. De Laat B, Derksen RH, Urbanus RT, De Groot PG. IgG antibodies that recognize epitope Gly40-Arg43 in domain I of beta 2-glycoprotein I cause LAC, and their presence correlates strongly with thrombosis. Blood 2005; 105; 1540–5.

70. Iverson GM, Victoria EJ, Marquis DM. Anti-beta2 glycoprotein I (beta2GPI) autoantibodies recognize an epitope on the first domain of beta2GPI. Proc Natl Acad Sci USA 1998; 95; 15542–6.

71. Ioannou Y, Romay-Penabad Z, Pericleous C, Giles I, Papalardo E, Vargas G, Shilagard T, Latchman DS, Isenberg DA, Rahman A, Pierangeli S. In vivo inhibition of antiphospholipid antibody-induced pathogenicity utilizing the antigenic target peptide domain I of beta2-glycoprotein I: proof of concept. J Thromb Haemost. 2009;7;5;833-42

72. Tuthill JI, Khamashta MA. Management of antiphospholipid syndrome. Journal of autoimmunity. 2009; 33;2;92-98.

73. Branch DW, Peaceman AM, Druzin M, Silver RK, El-Sayed Y, Silver RM, et al. A multicenter, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. The Pregnancy Loss Study Group. American journal of obstetrics and gynecology. 2000; 182;122-127.

74. Triolo G, Ferrante A, Ciccia F, Accardo-Palumbo A, Perino A, Castelli A, et al. Randomized study of subcutaneous low molecular weight heparin plus

aspirin versus intravenous immunoglobulin in the treatment of recurrent fetal loss associated with antiphospholipid antibodies. Arthritis and rheumatism. 2003; 48;3;728-731.

75. Sciascia S, Giachino O, Roccatello D. Prevention of thrombosis relapse in antiphospholipid syndrome patients refractory to conventional therapy using intravenous immunoglobulin. Clinical and experimental rheumatology. 2012; 30;3;409-413.

76. Tenti S, Guidelli GM, Bellisai F, Galeazzi M, Fioravanti A. Long-term treatment of antiphospholipid syndrome with intravenous immunoglobulin in addition to conventional therapy. Clinical and experimental rheumatology. 2013; 31;6;877-882.

77. Tyndall A. Successes and failures of stem cell transplantation in autoimmune diseases. Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program. 2011; 2011;280-284.

78. Statkute L, Traynor A, Oyama Y, Yaung K, Verda L, Krosnjar N, et al. Antiphospholipid syndrome in patients with systemic lupus erythematosus treated by autologous hematopoietic stem cell transplantation. Blood. 2005; 106;8;2700-2709.

79. Owaidah TM, Maghrabi K, Elkarouri MA, Al Mohareeb F, Al Harthi A, Al Zahrani H. Successful treatment of a case of catastrophic antiphospholipid syndrome with autologous BMT: case report and review of literature. Bone marrow transplantation. 2011; 46;4;597-600.

80. Hashimoto N, Iwasaki T, Sekiguchi M, Takatsuka H, Okamoto T, Hashimoto T, et al. Autologous hematopoietic stem cell transplantation for

refractory antiphospholipid syndrome causing myocardial necrosis. Bone marrow transplantation. 2004; 33;8;863-866.

Figure 1. Proposed target approaches for APS. (1) Depletion of B cells by anti CD20 monoclonal antibodies, to reduce pathogenic aPL; (2) Use of small inhibitory peptides modelled on domain V (TIFI) or domain I of β2GPI; (3) blocking of aPL/ β2GPI receptors on target cells (annexin A2 and Toll-like receptor 4 on endothelial cell and monocytes; lipoprotein receptor-related protein family on platelets; (4) inhibitors of complement components (5) inhibitors of intracellular pathway (p38MAPK and NF-kB), including BIRB796 BS, SB203580, VX702; (6) reducing arachidonic acid (AA) production inhibiting cytosolic phospholipases A2 (cPLA2) is one of the proposed antithrombotic mechanisms of hydroxychloroquine (7) Tissue factor inhibitors, including ACE inhibitors, pentoxifylline, an adenosine uptake inhibitor (dilazep), and ss-deoxyribonucleic acid derivatives (e.g, defibrotide) and newly developed anti-TF monoclonal antibodies; (8) New generation anticoagulants targeting FXa or thrombin.