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Review

Management of refractory anti-phospholipid syndrome

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ABSTRACT

Anti-phospholipid syndrome (APS) is an autoimmune prothrombotic disorder characterised by the predisposition to venous and/or arterial thrombosis and obstetric morbidity. Management of APS centres on attenuating the procoagulant state whilst balancing the risks of anticoagulant therapy. Cases of recurrent thromboses and obstetric complications occur despite optimum therapy. Alternative therapies for refractory cases are subject to disparity among clinicians due to the current lack of clinical evidence present. This review aims to address the current management strategies for refractory thrombotic and obstetric cases and future therapeutic interventions. The role and current clinical evidence of using long term low molecular weight heparin (LMWH) as an alternative to warfarin therapy for refractory thromboses is evaluated. Potential alternatives for thromboses including statins, hydroxychloroquine, Rituximab are reviewed as well as the additional avenues to target in the future as the pathogenic mechanisms of APS are unveiled. The optimal management for refractory obstetric APS cases is subject to controversy. This review focuses and assesses the current evidence for the uses of low dose prednisolone, intravenous immunoglobulin and hydroxycholoroquine in obstetric cases. The treatment modalities for the management of refractory APS require further clinical evidence.

Contents

1. Introduction

Anti-phospholipid syndrome (APS) is an autoimmune prothrombotic disorder characterised by the predisposition to venous and/or arterial thrombosis and obstetric morbidity. The latter encompasses recurrent miscarriages in the first trimester, fetal death in the second or third trimester, or severe pre-eclampsia. Anti-phospholipid antibodies (aPL) include lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti-β2-glycoprotein-1 (anti-β2-GP1) [1].

Antiphospholipid antibodies promote the activation of endothelial cells, monocytes and platelets. Endothelial cell activation by anti-β2-GP1 results in the upregulation of intracellular cell adhesion molecule-1 (ICAM-1) and tissue factor (TF). Monocyte activation additionally contributes to TF upregulation. Anti-β2-GP1 mediated platelet activation results in increased synthesis of thromboxane A2 which is mediated by nuclear factor κB (NFκB) and p38 mitogen-activated protein kinase (p38 MAPK). The resultant increased TF and thromboxane A2 expression thereby induces a procoagulant state. Moreover, the interaction of aPL with proteins such as prothrombin, factor X, protein C and plasmin involved in the clotting haemostasis may impede procoagulation factor inactivation and fibrinolysis. Additionally, aPL activates the complement cascade which contributes to the increased expression of TF and thus culminates in a heightened procoagulant state [2–4].

The management of APS centres on attenuating the procoagulant state whilst balancing the risks of anticoagulant therapy [5]. Treatment is determined by previous thrombotic events and aPL positivity. Primary prevention is pertinent in asymptomatic aPL positive patients, individuals with systemic lupus erythematosus (SLE) or in obstetric APS. Low-dose aspirin is recommended for

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primary thromboprophylaxis and is used in combination with hydroxychloroquine for patients with SLE and persistently positive LA and/or aCL. Individuals with APS who have had a previous thrombotic event require secondary thromboprophylaxis. This predominately entails warfarin therapy for thrombotic APS, to attain a target INR (international normalized ratio) of 2.0–3.0 with indefinite anticoagulation for patients presenting with a first venous event. Intensity of treatment is increased in patients with arterial disease and/or recurrent events to achieve a target INR of greater than 3.0.

Recurrent thromboses and obstetric complications have been reported to occur despite optimum therapy. Alternative therapies have been suggested but are subject to disparity among clinicians due to the paucity of clinical evidence. This review aims to address the current management strategies for thrombotic and obstetric refractory cases and possible future avenues that can lead to novel therapeutic interventions for refractory APS [4].

2. Management of refractory thrombosis

Despite strict prophylactic regimes, a proportion of patients do succumb to recurrent thrombotic episodes. As APS yields significant morbidity [6], early identification of patients that are refractory to treatment would be pertinent. This would permit careful vigilance and implementation of alternative treatment to prevent thrombotic recurrence.

Recurrent thromboses have been noted to occur in patients who are on optimum therapeutic warfarin [7]. Current recommendations dictate an INR between 2.0 and 3.0 as moderate intensity anticoagulation in patients with previous venous thrombosis. To counteract the recurrence of thromboses it has been previously proposed to raise the therapeutic INR range above 3.0. However, this was deemed ineffective since the RCTs conducted by Crowther et al. and Finazzi et al. which compared conventional anticoagulation (INR of 2.0 to 3.0) and high intensity (above 3.0) found no difference [8,9]. Furthermore, increasing the therapeutic INR range inherently increases the risk of bleeding and therefore becomes an unfavourable option [10]. The risk of severe bleeding in APS patients on anticoagulants is 2.0–3.0% per annum and thus serves as an additional difficulty in management of APS [5,11]. Nonetheless, it is important to note that the systematic review conducted by Ruiz-Irastorza et al. concluded that the frequency and risk of mortality for recurrent thrombosis is far greater than the risk of warfarin induced haemorrhage [12].

The management of these patients has been subject to disparity among clinicians in the past; a recent evidence-based consensus guideline formulated at the 13th International Congress on Antiphospholipid Antibodies states that long term low molecular weight heparin (LMWH) may be a safe and an efficient alternative to warfarin [13]. This is largely secondary to its dose-independent clearance, lowered affinity to heparin binding protein and excellent bioavailability. In addition to these characteristics, LMWH has recently been found to impede the hypercoaguable state present in patients with APS [14].

The use of LMWH as alternative therapy first came to light by Bick et al.'s study where dalteparin was administered over a long term period in APS patients resistant or intolerant to warfarin. The subjects in this study did not experience recurrent thromboses or adverse effects [15]. Similarly, two case reports by Dentali et al. demonstrated an efficient response to long term LMWH in patients with APS refractory to warfarin therapy [7]. On the contrary, another case study reported the use of enoxaparin subsequent to refractory warfarin therapy which resulted in a widespread pulmonary embolism after two months [16]. Nonetheless, as there is limited evidence on the safety profile and efficacy of long term LMWH; a recent retrospective study by Vargas–Hitos et al. evaluated 23 patients with refractory APS aimed to elucidate this. The study revealed that long-term LMWH therapy for a median duration of 36 months is safe and an effective alternative to vitamin K antagonists. This is reflected in 39% of patients who reported no recurrent episodes with a good quality of life, followed by 48% of patients who reported partial clinical improvement with an absence of recurrent episode [17]. Thus LMWH may indeed serve as a potential alternative to warfarin. However further studies and clinical trials are warranted to assess the long term use of LMWH therapy in refractory APS.

Despite its promising potential therapeutic role in refractory APS; LMWH does harbour limitations. It is subcutaneously administered and is responsible for heparin-induced thrombocytopenia (HIT) and osteoporosis. The latter is secondary to long-term therapy. Additionally, both LMWH and warfarin have multiple targets within the coagulation cascade. Therefore, this highlights the need for novel anticoagulants that are selective for a direct single target with a safer side effect profile. Dabigatran etexilate and rivaroxaban are orally administered agents that are currently licensed for use in the UK and Europe as prophylactic therapy for venous thromboembolism in patients undergoing total knee replacement or elective total hip replacement. Prospective randomised control trials that have been previously conducted have shed light on the possibility of utilizing these agents as prophylaxis for systemic embolism or stroke in acute coronary syndromes or in patients with atrial fibrillation (AF). Thus, one can postulate that these agents may additionally play a role as alternative thromboprophylaxis in APS management [18].

Dabigatran etexilate is a competitive direct thrombin inhibitor (DTI) which binds and abrogates its subsequent interaction with substrates; this ultimately leads to inhibition of fibrin formation and thrombin-induced platelet aggregation in addition to suppression of factors V, VIII, XI and XIII. Moreover, the anticoagulant response is more predictable with DTIs when compared to LMWH as it does not bind to plasma proteins. DTIs also have the ability to bind directly to clot-bound thrombin and are unlikely to cause HIT [18]. These characteristics collectively highlight dabigatran as a favourable alternative to LMWH. The efficacy of dabigatran in comparison to enoxaparin was assessed in three non-inferiority double-blind, randomised control trials in patients undergoing total hip replacement, knee replacement and knee arthoplasty; named RE-NOVATE, RE-MODEL and RE-MOBILIZE respectively [19–21]. Both RE-NOVATE and RE-MODEL trials revealed that dabigatran was non-inferior to enoxaparin [19,20]. Conversely, the RE-MOBILIZE trial failed to demonstrate non-inferiority [21]. Nonetheless, a meta-analysis of RE-NOVATE and RE-MODEL supported the conclusions drawn from these trials [22]. Furthermore, dabigatran was compared with warfarin in patients who had AF with a high risk of stroke in a randomised non-inferiority trial (RE-LY). Dabigatran was demonstrated to be non-inferior to warfarin in this instance [23].

Rivaroxaban is a direct competitive FXa (factor Xa) inhibitor which is orally administered. It is highly selective for FXa unlike LMWH which acts in an indirect manner. Rivaroxaban inhibits clot-associated FXa in addition to FXa within the prothrombinase complex. As FXa is an upstream molecule in the clotting cascade, its inhibition leads to the early blockade of coagulation [18]. Thus, these features of rivaroxaban reflect its potential as an alternative to LWMH. Furthermore, four double-blind RCTs (RECORD 1, 2, 3, 4) aimed to elucidate the efficacy of rivaroxaban in comparison to enoxaparin in patients undergoing elective hip or knee replacements [24–27]. The first three trials deduced that rivaroxaban was superior to enoxaparin in reduction of DVT, non-fatal PE or death [24–26]. The last trial demonstrated significantly lower proportion of patients with venous thromboembolism (VTE) than those on a higher dose of enoxaparin [27].

Thus, evidence from clinical trials using dabigatran or rivaroxaban is suggestive of its potential role as alternative thromboprophylaxis to LMWH or warfarin. Additionally, both agents do not require laboratory monitoring which further contributes to its array of advantages in comparison to conventional anticoagulation [18]. A trial with rivaroxaban is currently being negotiated. The results from this trial and any