ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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The Use of Direct Oral Anticoagulants in Antiphospholipid Syndrome

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H&O What is antiphospholipid syndrome, and what causes it?

HC Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia that is characterized by thrombosis and/or pregnancy morbidity in association with antiphospholipid antibodies (aPL).[1] The thrombotic manifestations encompass venous, arterial, or microvascular forms of thrombosis; approximately 50% of thrombotic events are deep venous thrombosis of the lower limbs or pulmonary embolism and 30% are stroke or transient ischemic attack.[2] APS-associated pregnancy morbidity includes recurrent early unexplained miscarriages, fetal death after 10 weeks' gestation, and premature delivery before 34 weeks' gestation because of preeclampsia/eclampsia or placental insufficiency (which leads to fetal growth restriction).[1]

The overall prevalence of APS has been estimated at 40 to 50 per 100,000 people,[3] with a female-to-male ratio of approximately 5:1.[2] Catastrophic APS, which accounts for approximately 1% of APS cases and has an overall mortality rate of 37%, is the most severe form of APS, with multiple organ thromboses. It usually involves small vessel thrombosis and develops over a short period.[4] Approximately 15% of patients with systemic lupus erythematosus have APS, in which case the disease is associated with organ damage and a more complicated course.[5]

Despite clear associations between aPL and thrombosis, as well as pregnancy morbidity, the pathophysiology of these complications is not well defined. More than one pathophysiologic process is likely involved. Family and population studies suggest a genetic predisposition to APS that appears to be both human leukocyte antigen (HLA) system–related and non–HLA-related. A key initiating process in the pathophysiology of thrombotic APS is binding of the β2 glycoprotein I (β2GPI) to exposed, negatively charged phospholipids. The resulting exposure of a cryptic domain 1 Arg39-Arg43 epitope is recognized by pathologic aPL. The Arg39-Arg43-aβ2GPI complex subsequently interacts with surface receptors, with activation of endothelial and inflammatory cells, causing prothrombotic and proinflammatory hemostatic changes. Placental thrombosis is not universal in obstetric APS, suggesting that other mechanisms are implicated. β2GPI is physiologically present on decidual endothelium and trophoblasts, and aPL-β2GPI complexes may lead to potentially damaging effects on fetal development. These include binding to trophoblasts, which inhibits their proliferation and differentiation, and the induction of trophoblast apoptosis. Other effects include antiangiogenic capacity with defective spiral artery development; binding to decidual cells and extravillous trophoblasts and inducing inflammatory responses; and activation of the complement system, leading in turn to activation of the coagulation system.

H&O How is APS diagnosed?

HC The international consensus (Sapporo/Sydney) classification criteria for APS require the presence of thrombosis or pregnancy morbidity in association with 1 or more of the following: persistent (defined as present on ≥2 occasions ≥12 weeks apart) lupus anticoagulant (LA), medium or high titer immunoglobulin G (IgG) or immunoglobulin M (IgM) anticardiolipin antibodies (aCL), or anti-β2GPI.[1] LA is thought to carry the highest

risk of all the aPL for thrombosis and has been reported to be the primary predictor of adverse pregnancy outcome in patients with aPL. However, ensuring accurate LA testing can be challenging. This problem was highlighted in a recent International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardisation Committee (SSC) survey. The survey showed that good agreement exists on several key recommendations in the ISTH and other guidelines regarding LA testing, including sample processing, principles of testing, choice of tests, repetition of LA testing to confirm persistent positivity, and the use of interpretative reporting. However, less agreement exists regarding some other aspects, including the timing of testing in relation to thrombosis or pregnancy, testing in patients on anticoagulant therapy, cutoff values, and calculation and interpretation of results.[6] ISTH guidance on these issues is in preparation.

> Effective and safe anticoagulation in APS remains an unmet need.

The international consensus criteria, which are currently being updated under the auspices of the American College of Rheumatology and the European League Against Rheumatism (EULAR),[7] were designed for scientific clinical studies rather than for diagnosis in routine clinical practice. Many other clinical manifestations are associated with persistent aPL, including immune thrombocytopenia, livedo reticularis, migraine, valvular heart disease, and cognitive dysfunction, and patients with these noncriteria manifestations of APS require clinical attention. In addition, noncriteria obstetric manifestations occur, including low titer (<99th percentile) positivity for aCL and anti-β2GPI and/or clinical criteria such as 2 (rather than 3 consecutive) miscarriages, late preeclampsia or premature birth (after 34 weeks' gestation), and 2 or more unexplained in vitro fertilization failures. Limited studies, most of them retrospective, suggest that some women with noncriteria obstetric APS may have successful pregnancy outcomes following standard treatment with low-dose aspirin and low-molecular-weight heparin (LMWH), although substantive data are lacking.[8]

H&O What is the standard treatment for APS?

HC Warfarin or other vitamin K antagonists (VKAs) are standard therapy for the treatment and secondary thromboprophylaxis of thrombotic APS.[9-14] However, VKAs have a slow onset of action of several days, a narrow therapeutic window, numerous drug and dietary interactions, and the potential for variation of action in the presence of alcohol, intercurrent illness, exercise, and smoking. Patients on VKAs require regular monitoring of the international normalized ratio (INR). The numerous interactions between VKAs and other drugs, which may increase or decrease the INR, are particularly undesirable in patients who have APS with concomitant systemic lupus erythematosus, who invariably require many agents for disease control. Thus, effective and safe anticoagulation in APS remains an unmet need.

Standard-intensity VKA therapy—that is, with a target of INR of 2.5—is used in patients who have APS with a first episode of unprovoked venous thromboembolism (VTE). Indefinite anticoagulation, as in the general population,[15] is advised for patients who have APS with an unprovoked VTE.[9,14] Persistent aPL have been shown to be associated with recurrent VTE when anticoagulation has been stopped following a negative D-dimer test result after a first unprovoked VTE, with odds ratios higher for patients with double or triple aPL positivity. This finding supports anticoagulation therapy for an extended duration in patients who have APS following a first unprovoked VTE. Data are lacking to guide the optimal duration of anticoagulation for patients who have APS with a provoked VTE, in whom persistent aPL constitute an ongoing prothrombotic risk factor. The optimal anticoagulation intensity for APS associated with arterial thrombosis is uncertain, with variability in the guidelines. The recent European League Against Rheumatism (EULAR) guidelines recommend standard-intensity VKA therapy, with or without low dose aspirin, or high-intensity VKA therapy, with a target INR of 3.5.

H&O How often are direct oral anticoagulants used in APS?

HC A systematic review suggests that aPL are present in 10% of patients with deep venous thrombosis.[16] Although this should be confirmed in appropriately designed population studies, it suggests possible underdiagnosis of APS. It also implies that patients with APS were probably included in the phase 3 randomized controlled trials (RCTs) of direct oral anticoagulants (DOACs) in patients with VTE, although aPL status was not systematically documented in these trials. It is estimated that 1 to 2 per 1000 of the population are affected by VTE. Thus, many patients with a first VTE who have started a DOAC, the current standard of care for patients after a first VTE, probably have undiagnosed APS, given that the diagnosis requires the demonstration of persistent positivity for aPL

on 2 occasions at least 12 weeks apart.[1] Furthermore, testing for aPL in patients with an unprovoked VTE event is not universally recommended, and it is not addressed in the most recent American College of Chest Physicians guidelines on antithrombotic therapy for VTE disease.[15]

The European Medicines Agency (EMA) recommendation against the use of DOACs, especially in patients who have APS with triple positivity for aPL,[17] has increased caution with regard to their use in patients with thrombotic APS. As a result, testing for aPL following a first unprovoked VTE can inform decisions about anticoagulation options. The EMA recommendation followed a risk assessment by the EMA Pharmacovigilance Risk Assessment Committee triggered by the TRAPS (Rivaroxaban in Thrombotic Antiphospholipid Syndrome) RCT.[18] The EMA recommendation has been incorporated into the DOAC manufacturers' summary of product characteristics and is being introduced in countries beyond the European Union, including the United States. The United Kingdom's Medicines and Healthcare products Regulatory Agency has issued the following advice to healthcare professionals: "Review whether continued treatment with a DOAC is appropriate for patients diagnosed with antiphospholipid syndrome, particularly high-risk patients, and consider switching to a vitamin K antagonist such as warfarin."[19]

> The main disadvantage when considering DOAC use in APS is that the optimal approach is not yet established.

H&O What are the advantages and disadvantages of using DOACs in APS?

HC DOACs have emerged as the standard of care in several thrombotic conditions, on the basis of large phase 3 RCTs in the general population. DOACs have several advantages compared with VKAs. They are administered in fixed doses and provide effective anticoagulation within hours of administration, so initial bridging anticoagulation with LMWH is not required. DOACs have a more predictable anticoagulant effect than VKAs do, and patients therefore do not require routine anticoagulant monitoring. DOACs have fewer drug interactions than VKAs do and no interactions with food or alcohol. The main disadvantage when considering DOAC use in APS is that the optimal approach is not yet established.

H&O What recent studies have examined the use of DOACs in APS?

HC Evidence about the efficacy and safety of DOACs in APS is limited. A post hoc analysis of patients with APS included in 3 RCTs of treatment with dabigatran (Pradaxa, Boehringer Ingelheim) vs warfarin in the general population showed no differences in outcomes between dabigatran and warfarin.[20]

The randomized controlled RAPS (Rivaroxaban in Antiphospholipid Syndrome) trial compared rivaroxaban (Xarelto, Janssen) at 20 mg once daily vs standard-intensity warfarin in 116 patients following a single or recurrent VTE event while they were on no anticoagulation or subtherapeutic anticoagulation. No thrombotic or bleeding events occurred during 7 months of follow-up in either treatment group. Patients on rivaroxaban had a significantly better quality of life. Of note, 28% of the patients (24.6% in the rivaroxaban arm and 32.2% in the warfarin arm) had triple positivity for aPL, and those with APS-associated arterial thrombosis were excluded.[21] The results suggest that rivaroxaban offers the potential to be an effective alternative to VKAs in patients with thrombotic APS who have a VTE requiring standard-intensity anticoagulation, although the trial was not powered for clinical outcomes.

The TRAPS trial, which compared rivaroxaban at 20 mg once daily vs standard-intensity warfarin in 120 patients with triple aPL positivity and thrombotic APS, was terminated prematurely after approximately 1 1/2 years following 7 recurrent thrombotic events, all arterial, in patients in the rivaroxaban arm vs none in the warfarin arm. Patients with a history of arterial thrombosis constituted 19% of the trial population and 57% of those with recurrent thrombosis. There were 6 major bleeds, 4 in the rivaroxaban-treated patients and 2 in those on warfarin (no significant difference), with predisposing risk factors for bleeding in 5 of these 6 cases.[18]

An RCT by Ordi-Ros and colleagues compared rivaroxaban at 20 mg daily vs VKA therapy at standard intensity (target INR, 2.0-3.0) or high intensity (target INR, 3.1-4.0) in 190 patients with thrombotic APS, approximately 60% of whom had triple aPL positivity. Recurrent thrombosis occurred in 11 (11.6%) patients in the rivaroxaban arm compared with 6 (6.3%) in the VKA group, with annualized recurrent thrombosis rates

of 3.9% vs 2.1%. The patients receiving rivaroxaban had 9 documented strokes, vs none in the VKA group. The authors concluded that rivaroxaban was not noninferior to dose-adjusted VKA therapy.[22]

The ASTRO-APS (Apixaban for Secondary Prevention of Thromboembolism Among Patients With Antiphospholipid Syndrome) RCT, with a revised protocol comparing apixaban (Eliquis, Bristol-Myers Squibb) at 5 mg twice daily vs standard-intensity warfarin in patients with APS and VTE requiring standard-intensity anticoagulation (ie, the "RAPS phenotype"),[23,24] is currently active but not recruiting.

A recent systematic review of 728 patients by Sanchez-Redondo and colleagues reported a recurrent thrombosis rate during DOAC treatment of approximately 11% per year. The following factors in patients on DOACs were associated with a high risk for recurrent thrombosis: a higher mean number of prior thrombotic events, a history of combined arterial and venous thrombosis, previous treatment with LMWH, use of immunosuppressant treatment, and no reason to switch anticoagulant treatment other than the patient's own decision. The authors reported that meta-analysis of the data from clinical trials did not show a statistically relevant difference in the risk for thrombosis or bleeding in a comparison of warfarin with DOACs, however this comparison was limited to 2 trials (RAPS and TRAPS) and 6 months of follow-up.[25] A previous meta-analysis of DOACs in APS, by Dufrost and colleagues, reported a recurrent thrombosis rate of approximately 11.7% per year in 447 patients with APS on DOACs. This study also identified an elevated risk for recurrent thrombosis in patients who experienced recurrent thrombosis while on VKAs, as well as in patients who had triple aPL positivity.[26]

H&O Have any other changes occurred regarding the role of DOACs in APS?

HC Guidance is emerging on the potential use of DOACs in patients with APS. This includes the 2019 EULAR recommendations for the management of APS in adults, which state that "rivaroxaban should not be used in patients with triple aPL positivity" because of the high risk for recurrent events, whereas DOACs "could be considered in patients not able to achieve a target INR despite good adherence to VKA or those with contraindications to VKA (eg, allergy or intolerance to VKA)."[14]

The EULAR guidelines also advise that switching patients from VKA to DOAC treatment owing to poor adherence to VKA treatment or INR monitoring should be avoided. An addendum to the existing British Society for Haematology guidelines[8] focused on DOAC use in APS, is anticipated. The ISTH SSC on Lupus Anticoagulant/Antiphospholipid Antibodies is currently preparing guidance for clinicians on the use of DOACs in patients with APS.

H&O Does more research need to be done, and of what type?

HC Further studies are required to determine the potential role of DOACs in APS. These studies need to take into account the clinical heterogeneity of APS and the laboratory aPL phenotype. Careful consideration of the optimal DOAC dosing, depending on the type of thrombosis, is also needed. For example, no precedent exists for the use of standard doses of DOACs in patients who have APS with arterial thrombosis, and evidence from RCTs and systematic reviews suggests that such patients are at increased risk for recurrent thrombosis while on DOACs. APS patients with recurrent thrombosis while on standard-intensity anticoagulation with VKAs require high-intensity anticoagulation, which, based on the limited data, is an option after a first arterial thrombosis.[14] The phase 3 trials of DOACs vs warfarin in the general population demonstrated efficacy of DOACs vs standard-intensity warfarin.[27] The doses of DOACs used in these studies may not provide sufficient protection against thrombosis in patients who require high-intensity anticoagulation. The phase 2/3 RISAPS trial (RIvaroxaban for Stroke patients with AntiPhospholipid Syndrome) aims to assess the efficacy of high-intensity rivaroxaban at 15 mg twice daily vs that of high-intensity warfarin, target INR 3.5, in patients who have APS with a history of stroke or other ischemic brain manifestations.[28] Future studies should also aim to establish whether DOAC therapy is appropriate in APS patients with a lower-risk thrombotic APS phenotype. An ISTH international registry of DOAC use in patients with APS is being set up with the intent to capture information on all DOAC use and outcomes in these patients.[29]

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