Update on Antiphospholipid Syndrome

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Abstract
Revised criteria for the antiphospholipid syndrome were published in 2006. Major changes from the 1999 criteria are an increase in the time between two laboratory studies required for diagnosis from 6 to 12 weeks, the acceptance of antibody to \( \beta_2 \) glycoprotein I as a criterion, the exclusion of older age persons, and the acknowledgment of several associated findings such as livedo, heart valve disease, and antibody to prothrombin.

New concepts of pathogenesis now invoke complement activation and participation of the innate immune system upstream to thrombosis. Warfarin remains the treatment of choice for patients who have suffered thrombosis, but antiplatelet agents and heparin are options. Target INR is 2.0-3.0. Treatment is potentially life-long, though options for withdrawal of treatment are under investigation.

In 1999 the first (Sapporo) Consensus Conference suggested classification criteria for the antiphospholipid syndrome (APS). In late 2004 a second (Sydney) conference considered the first 5 years of the use of these criteria and suggested revisions. These revisions, based on the argument that the syndrome is the same whether or not lupus or other rheumatic disease is present, changed the designations of primary and secondary APS to APS with or without associated rheumatic disease. The Sydney conference also recognized the separate conditions of catastrophic antiphospholipid syndrome (CAPS) and presence of antiphospholipid antibodies (aPL) with no associated symptoms. Other changes from the Sapporo criteria included extension of the time between first and second positive test to 12 weeks (from 6), exclusion of transient positivity due to infection, addition of antibody to \( \beta_2 \) glycoprotein I (\( \beta_2 \) GP-1), and recognition of features of the illness that can serve as diagnostic clues for individual patients but not as classification criteria for the purpose of clinical trials (livedo, thrombocytopenia, cardiac valve disease, renal thrombotic microangiopathy, and some research laboratory-identified antibodies) (Table 1). None of these changes alters the basic demographic findings of APS: 30% to 40% of SLE patients have aPL but only about 10% have APS, APS without associated disease constitutes about half of all APS, and CAPS is rare but lethal.

Mechanisms of Pathogenesis
Thrombosis is the most easily recognized manifestation of APS and the manifestation that is most easily explained by a mechanism: endothelial activation or injury leading to local activation of adhesion molecules and procoagulant proteins, leading to in situ and potentially embolic thrombus. Similarly, many investigators believe that placental thrombosis explains recurrent pregnancy loss. Other common clinical manifestations are less easily explained by thrombosis: livedo, hyperintense brain lesions on MRI, valve disease, thrombotic microangiopathy, and possibly leg ulcers. Even the mechanism of pregnancy loss is now in question.

A mouse model of pregnancy loss allows exploration of pathogenic mechanisms. Various mice, spontaneously or passively or actively immunized, develop features of APS: lupus anticoagulant, thrombocytopenia, and pregnancy loss (fetal resorption). When challenged under experimental conditions, mice develop larger and more sustained clots than do aPL-negative mice. The pregnancy
model is easiest to study. Untreated, aPL-positive mice lose about half their fetuses. Given heparin, the dams have pregnancies with near normal fetal survival rates. However, full anticoagulation with fondaparinux or hirudin does not protect the pregnancies; complement-deficient mice or those treated with complement inhibitors do have normal pregnancies. Since heparin inhibits complement, and since, in humans, sub-anticoagulant doses of heparin are effective treatment for recurrent pregnancy loss, the mouse experiments strongly suggest that the initial—and targetable—lesion is complement activation rather than coagulation, and that the clotting events are secondary. Mouse models of thrombosis are less clear-cut, but in these, too, complement must be present for thrombosis to occur. 2-4

Questions About Warfarin

Should Warfarin Be Used at All?

Although warfarin is the drug of choice for treatment of thromboembolism, warfarin may be inappropriate for many phenomena of the APS. Specifically, no data support its use in asymptomatic bearers of aPL, ie, patients who carry high-titer antibody for decades with no clinical event. In the AntiPhosphoLipid-Acetyl Salicylic Acid (APLASA) study, in which patients with aPL were randomized to 81 mg aspirin or placebo, at interim analysis the annual thrombosis event rate was 0.85% for the combined groups, with other risk factors (surgery, injury, oral contraceptive initiation) predicting the first event in those who did suffer thrombosis. 5 The complication rate of therapeutic warfarin is much higher than this event rate. In addition, no data indicate efficacy of warfarin in treatment of microangiopathic nephropathy, valvular heart disease, livedo reticularis, or leg ulcers. The concept that anticoagulation is a complete treatment for antiphospholipid syndrome is likely false.

How Much Warfarin Should Be Used?

Initially, standard warfarin doses (international normalized ratio [INR] 2.5) were thought sufficient for APS patients. Because some patients continue to suffer thromboses at this dose, some investigators advocate higher intensity therapy, up to a target INR of 3.5 or 4.0. Two recent controlled, blinded trials, 6,7 both with over 100 patients randomized to high or standard dose warfarin and followed for 2.7 and 3.6 years, found no benefit to the higher dose. In fact, in both studies the annual recurrence rate was 10.7% and 11.1% at a target INR of 3.5
(3.3 and 3.2 achieved) compared to 3.4% to 5.5% at a target INR of 2.5 (2.3 and 2.5 achieved). Controversy remains whether the lower dose applies to patients with arterial vs venous thromboses, or to those who have had recurrent thromboses while anticoagulated.

For How Long Should Warfarin Be Used?

Conventional wisdom, supported by several retrospective anecdotes, states that warfarin treatment should be lifelong. Studies in non-APS patients with thrombosis cite venous recurrence at risk 10%/year after stopping treatment after 3, 6, 12, or 24 months. The best available evidence from subgroup studies of these populations suggests that the recurrence risk may not be higher in patients with aPL. Furthermore, most studies of recurrence rate do not take other risk factors into account. Some patients eventually lose aPL positivity; others spend years with no recurrence after a ‘triggered’ thrombosis, the trigger being trauma including surgery, estrogen therapy, etc. Many investigators are now asking whether it might be possible to withdraw anticoagulation if trigger factors are no longer present. Studies addressing this question are just beginning.

Are There Alternatives to Warfarin?

Surprisingly little information is available about alternative anticoagulant or antiplatelet therapy for APS patients. In our retrospective experience with 54 patients followed for 2 or more years, recurrence rates were 5.4, 9.1, and 3.1 per 100 patient-years for aspirin, clopidogrel, and low molecular weight heparin, rates estimated (in the absence of formal controls) to be similar to recurrence rates in warfarin-treated patients.8 We, like others, have treated a few patients with rituximab. Four of six had apparent full recovery and two have had late response, possibly independent of treatment.9 Formal trials are under consideration.

Current Treatment Recommendations

Two groups have recently published treatment recommendations for APS.10,11 These recommendations are, in brief: for asymptomatic bearers of aPL, no treatment; for those with uncomplicated venous thrombosis, warfarin INR 2.0 to 3.0; for those with uncomplicated arterial thrombosis, warfarin INR 3.0; for those with recurrent thrombosis on therapeutic warfarin, warfarin INR 3.0 to 4.0 with low dose aspirin; and for those with CAPS, warfarin or heparin, corticosteroid, intravenous immunoglobulin and/or plasmapheresis. Treatment for pregnancy loss recommendations are asymptomatic (no prior losses), no treatment; single loss less than 10 weeks, no treatment; recurrent loss less than 10 weeks (no thrombosis) or single loss after 10 weeks, prophylactic dose heparin and low dose aspirin through 6 to 12 weeks postpartum; any prior thrombosis regardless of pregnancy loss history, therapeutic heparin plus aspirin through pregnancy, warfarin postpartum.

Not currently part of standard therapy, but used on theoretical grounds by some physicians, are hydroxychloroquine, the statin drugs, platelet-active drugs, thrombin inhibitors (primarily in patients suspected of having heparin-induced thrombocytopenia), and rituximab. Anecdotes and mechanistic theories, but no formal trials, support use of such agents in experimental or otherwise desperate circumstances. New investigations into mechanisms of APS, focusing primarily on endothelial cell or platelet activation and on complement activation, will produce additional therapeutic options in the future. Current work on microbial triggers may produce prevention opportunities as well.

References