Editorial

Antiphospholipid Antibody Syndrome: Further Evidence to Guide Clinical Practice?

In this issue of *The Journal*, Giron-Gonzalez and colleagues present new information about the natural history and management of patients with antiphospholipid antibodies (aPL)[1]. In a carefully performed, large prospective study these authors followed a cohort of patients with aPL and observed them for clinical manifestations that might be related to aPL. Patients were drawn from 2 groups: 226 patients had had a clinical manifestation attributable to aPL and thus had been diagnosed with the antiphospholipid antibody syndrome (APS), and 178 were discovered to have an aPL after being investigated for an inhibitor of their activated partial thromboplastin time (APTT). Patients underwent regular clinical followup for 36 months.

The study makes a number of important, novel observations. For example, the study found that about half of patients with an acute thrombosis (which led to the diagnosis of APS) had coincident risk factors for thrombosis; this observation confirms those in other settings where thrombosis is more common in patients with a combination of risk factors[2]. About two-thirds of patients with aPL and thrombosis had a venous thrombosis; this finding mimics that seen in other contemporary studies[3,4]. Finally, although mean platelet counts were similar in patients with APS and those with asymptomatic aPL positivity, the frequency of clinically important thrombocytopenia (defined in this study as a platelet count of less than 125×10^9/l) was higher in patients with symptomatic than in those with asymptomatic aPL (32 of 226 compared with 0 of 178, respectively; $p < 0.001$).

Over extended followup, a total of 12 recurrent thrombotic events occurred in the 133 patients with primary APS, while in the 93 patients with secondary APS, 4 recurrent thrombotic events occurred. Nine of the 12 recurrent events in patients with primary APS occurred in the first 3 months after diagnosis, and all 9 were fatal; one of the recurrent thrombi in the secondary patients occurred in the first 3 months and caused one of the 9 fatal events in these patients. Mortality in the group overall was not predicted by any of a series of baseline variables; however, the specific statistical techniques and markers used in this analysis are not discussed; thus the strength of any inferences drawn from this analysis is limited.

Four of 208 surviving patients with APS experienced major hemorrhage, all occurring when the international normalized ratio (INR) value was greater than 3.0. No patient with asymptomatic aPL (that is, an aPL detected as a result of investigations for an unexpected prolongation of the APTT) experienced thrombosis or pregnancy morbidity. This finding provides additional evidence that asymptomatic screening-detected aPL are of limited clinical relevance.

Perhaps the most valuable aspect of this study is the presentation of carefully collected prospective data on the behavior of aPL titer: over about 36 months of followup about one in 5 patients with an anticardiolipin antibody, and a smaller percentage of patients with a lupus anticoagulant, became seronegative for aPL. Confirming anecdotal experience, patients with higher titer anticentromere antibodies were less likely to become seronegative.

Although this study is valuable because it adds new information to the literature describing aPL, it does reach a number of unwarranted, potentially dangerous conclusions. The authors state that, "in asymptomatic aPL carriers a zero incidence of thrombotic episodes could be predicted if these specific measures of prevention are applied." Although there is no doubt that, irrespective of aPL presence, the application of appropriate antithrombotic therapy reduces the risk of thrombosis in patients at moderate or high risk of this complication, a prospective cohort study cannot provide evidence of therapeutic efficacy. Thus it is wrong to conclude from this study that antithrombotic prophylaxis prevented thrombosis: patients may not have been destined to have this complication and, in fact, the use of inappropriately intensive antithrombotic prophylaxis (for example, the use of high dose prophylaxis, 1 mg/kg, as described by the authors) may cause avoidable bleeding complications in such patients. To prove their assertion of therapeutic efficacy, the authors would need to test their hypothesis in a properly performed randomized clinical trial. The low risk of thrombosis coupled with the low

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incidence of significant thrombocytopenia in these patients does, however, support the hypothesis that asymptomatic aPL are likely relatively unimportant.

Most contentiously, the authors state that their observations support the use of "higher intensity warfarin." As discussed in the previous paragraph, the results of a cohort study cannot prove therapeutic efficacy, and the study does not mention the results of 3 recent methodologically rigorous studies, all of which support the hypothesis that such patients are optimally treated with less, rather than more, intensive anticoagulant therapy. Our group[3] and Finazzi, *et al*[4] have performed randomized clinical trials in patients with APS who were allocated to standard (target INR 2.0 to 3.0) or high intensity (target INR 3.0 to 4.0) warfarin. Both studies found that the overall risk of recurrent thrombosis was very low, and was lower in patients allocated to standard intensity warfarin than in those allocated to high intensity warfarin. Taken in combination, these studies support the hypothesis that warfarin administered with a target INR of 2.0 to 3.0 should be considered "standard therapy" in all patients with APS who have not had recurrent thrombosis while they were taking warfarin therapy. This argument was recently bolstered by the results of the APASS-WARSS study[5]; this large randomized trial was unable to find evidence either that patients with APS had a higher risk of recurrent stroke than patients without APS, or that warfarin therapy was superior to aspirin therapy for secondary prevention of stroke in such patients.

Despite these limitations, the study represents an important addition to the current literature in this area, and taken in concert with other recent, methodologically rigorous studies, provides additional evidence to guide evidence-based treatment of patients with aPL.

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