Aspirin thromboprophylaxis of asymptomatic antiphospholipid-positive subjects

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The appropriateness of aspirin prophylaxis to prevent the occurrence of thrombosis in asymptomatic patients with confirmed positivity of antiphospholipid antibodies (aPL) has been recently debated. On the one side, Meroni and his group [1] support the reasons in favor of aspirin administration, particularly to patients considered at high risk of thrombosis. These patients are identified as those suffering from systemic lupus erythematosus, rheumatoid arthritis or other autoimmune diseases, those carrying other acquired or congenital pro-coagulant risk factors and elderly subjects. On the opposite side, Finazzi [2] proposes the reasons against aspirin prophylaxis, underlying the paucity of data coming from well-designed clinical studies and the need for such trials, particularly in patients with autoimmune diseases or with special aPL patterns, who may be at higher risk of thrombosis.

In this letter, I would like to pinpoint a few issues to help the debate.

The presence of risk factors of thrombosis increases the risk of first event of aPL-positive patients. Regarding the acquired, often modifiable risk factors, i.e., diabetes, blood hypertension and hypercholesterolemia, their control is of the utmost importance. This, together with the administration of short courses of antithrombotic treatment in the case of surgery, trauma or prolonged immobilization, may abate the risk of developing the initial thrombosis, as prospectively demonstrated by Giron-Gonzalez and co-workers in a large group of aPL-positive subjects [3]. With respect to the most frequent congenital risk factors of thrombosis, a retrospective study investigated the prevalence and clinical correlations of the G1691A mutation of factor V gene, the G20210A mutation of factor II gene and the C677T mutation of methylenetetrahydrofolate reductase gene in a large cohort of aPL-positive Italian patients [4]. The prevalences of these mutations are similar to those of the general population and only the heterozygosity for the G1691A mutation of factor V gene is significantly associated with venous thrombosis. No correlation is found with arterial thrombosis. Since the prolonged administration of aspirin did not significantly reduce the occurrence of an initial venous thrombosis in the Women’s Health Study [5], it is of questionable value to propose aspirin prophylaxis for aPL-positive subjects who carry a congenital risk factor of (venous) thrombosis.

Age cannot be considered, by itself, a risk factor for thrombosis sufficiently strong enough to warrant aspirin prophylaxis in aPL-positive patients. Indeed, elderly people have a state of hypercoagulability, characterized by heightened coagulation enzyme activity, enhanced formation of fibrin and secondary hyperfibrinolysis, high plasma concentrations of fibrinogen and factor VIII [6]. However, these abnormalities were demonstrated in a group of healthy centenarians, who never suffered from thrombosis in their life. On the opposite side, elderly people may have increased risk factors of hemorrhage, which also calls for caution when aspirin is used.

Next, it is important to underline that different aPL antibodies confer different risks of thrombosis. Lupus anticoagulants (LAC) consistently shows the highest strength of association with arterial and venous thrombotic complications in both adults and children [7]. Anticardiolipin (aCL) and anti β2-glycoprotein I (aβ2-GPI) antibodies are less strongly associated, even though the former antibodies represent a possible risk factor for arterial
thrombosis when present at high titer and the latter ones for venous thrombosis [8]. In recent years, some groups show a stronger association between thrombosis and the presence of multiple positive aPL tests when compared to a single positive test. LAC is a laboratory phenomenon caused by the anticoagulant effect of αβ2-GPI and anti-prothrombin antibodies (aPT), which may be present alone or in combination [9]. In other words, LAC is a measure of the functional activity of subgroups of αβ2-GPI and aPT, which explains the partial overlap between LAC, aCL and αβ2-GPI on the one side and between LAC and aPT on the other. In the past few years, tests have been developed to distinguish between αβ2-GPI-dependent and aPT-dependent LAC [10, 11]. Only the former antibodies are consistently associated with thrombosis [12]. A further characterization of the αβ2-GPI-dependent LAC activity has been recently provided. IgG αβ2GPI with LAC activity recognizes the sequence of Gly40-Arg43 within domain I and ELISAs are being developed to specifically pick up these pathological antibodies [13]. Thus, future clinical trials will have to stratify aPL-positive asymptomatic patients according to their antibody profile. Due to the low prevalence of aPL-positivity among the general population, which has been estimated to range between less than 1% to about 7% [14, 15], these trials will be successful only in an international, multicentre setting.

Conflict of interest statement The author declares that she has no conflict of interest related to the publication of this manuscript.

References