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8

The treatment of antiphospholipid syndrome: A harmonic contrast

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The antiphospholipid syndrome (APS) is characterized by a wide variability in clinical manifestations. Recommendations for therapy are conditioned by the lack of appropriate studies, due either to methodological limitations or excessive selection of patients. There is consensus in treating patients with APS and first venous thrombosis with warfarin to a target international normalized ratio (INR) of 2.3–3.0. However, a recent systematic review including observational studies found patients with APS and stroke to be at a high risk of recurrent events. We thus recommend a target INR $>$ 3.0 in this group. Likewise, the optimal approach for women with obstetric manifestations of APS is not completely defined; some authors recommend universal aspirin plus heparin whereas others consider aspirin in monotherapy useful for women with recurrent early miscarriage only. Correction of vascular risk factors and a high-risk management of pregnancy, including Doppler studies of the uterine and umbilical vessels, are warranted. Hydroxychloroquine and statins are likely to become important in the future.

Key words: anticardiolipin; fetal death; lupus anticoagulant; miscarriage; preeclampsia; stroke; thrombosis.

ANTIPHOSPHOLIPID SYNDROME: CLINICAL VARIABILITY AND THE WEIGHT OF EVIDENCE

In the early 1980s, the antiphospholipid syndrome (APS) was described as a unique form of autoantibody-induced thrombophilia.[1] Over the last 20 years, clinicians have become aware of the importance of this condition, which typically leads to recurrent thrombotic

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events, mainly in young adults, as well as to several obstetric complications such as miscarriage, fetal loss and severe preeclampsia. However, the clinical spectrum of APS has expanded with a growing number of manifestations in which thrombosis plays a central role.[2]

Such a clinical variability makes it difficult to formulate universal therapeutic recommendations for patients with APS. Some clinical manifestations are uncommon, so that only anecdotal experiences are available, such as the case of antiphospholipid antibody (aPL)-related intracranial hypertension.[3] Moreover, different combinations of venous, arterial, and obstetric events are the rule, and it is not known why some patients experience thrombosis on only one vascular bed whereas others have both venous and arterial events, or an obstetric syndrome combined (or not) with thrombosis, or why many patients with aPL remain asymptomatic for life. In other words, it is almost impossible to predict who will present with clinical manifestations, and which these will be. However, there is a tendency for events to recur, that is, people with venous or arterial thromboses usually have new thrombosis in the same vascular bed and women with APS and miscarriage often have subsequent pregnancy losses if left untreated.[4,5]

As commonly occurs in the field of systemic autoimmune diseases, the initial studies in APS were observational cohorts in which the different therapeutic groups were not randomized.[6,7] It was after the publication of these series that the recommendation of prolonged (indefinite) anticoagulant treatment of thrombosis in APS ensued, probably with a higher intensity of anticoagulation.[8,9] Over the following years, higher-quality studies were published, including two randomized controlled trials (RCTs)[10,11] and a systematic review.[12] These aimed to confirm or refute results obtained by observational studies. Likewise, observational series[13–15] were followed by RCTs[16,17] in the field of miscarriage secondary to APS. Recently, a systematic review of the Cochrane collaboration on the prevention of recurrent miscarriage in women with aPL has been published.[18] Thus, at this point, a growing body of evidence is available.

Evidence, however, is not always synonymous with truth. Unfortunately, observational and experimental studies have often reached different conclusions with regard to some important issues. Whereas optimal therapy is best defined by RCTs, in relatively infrequent conditions such as APS it is difficult to recruit a large group of patients representing the whole spectrum of the syndrome and willing to participate in studies. Although methodologically weaker, observational series have the potential advantage of the larger size and the inclusion of non-selected, 'real-world' patients. Such studies have been paramount in the study of systemic lupus erythematosus (SLE) and other autoimmune diseases.[19] Thus, any information available is potentially useful and the final conclusions must take into account both methodological and population-based limitations.

MANAGEMENT OF THROMBOSIS IN ANTIPHOSPHOLIPID SYNDROME

Evidence and discrepancy

In 2006, Lim et al published a systematic review focused on the therapeutic aspects of APS.[12] The final recommendations with regard to thrombosis are shown on Table 1. It is noteworthy that, despite the title of the paper (Management of antiphospholipid antibody syndrome: a systematic review), the treatment algorithm refers to patients with antiphospholipid antibodies, with no specific mention of the management of patients with stroke and persistently positive aPL appearing in the text. In summary, the authors recommend that patients with aPL suffering a venous or non-cerebral arterial