43 Management of Thrombosis in Antiphospholipid Syndrome

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Introduction

Among the growing variety of clinical manifestations of antiphospholipid syndrome long-term prognosis is most influenced by the risk of recurrent thrombosis in APS. Therefore, the most important aspects concerning management of patients with APS are treating thrombosis, preventing re-thrombosis (i.e., secondary prophylaxis) and, ideally, reducing the number of individuals having aPL who develop the syndrome (i.e., primary prophylaxis).

Unfortunately, the optimal therapy for each of these scenarios has not been yet defined. The paucity and relative low quality of the studies performed, mainly due to selection criteria of patients, lies behind the lack of agreement among authors. These discrepancies have been recently shown in the consensus documents published after the 10th Conference on Antiphospholipid Antibodies held at Taormina, Sicily, in September 2002 [1–3].

However, important advances have taken place during the past few years, and, specifically, since the first edition of this text was published in 2000. Therefore, this chapter deals with the task of presenting available data, discussing their strengths and limitations and defining the arguable position of these authors on conflicting issues.

Treatment of Thrombosis in APS: Acute Therapy and Secondary Prophylaxis

The description of APS by Hughes in 1983 [4] provided a new insight into vascular disease. Here, for the first time, was a common prothrombotic disorder which resulted in arterial as well as venous thrombosis. Treatment of the acute thrombotic event, if identified, is no different in APS than in the general population. Patients with venous thromboembolism are given heparin (currently low-molecular-weight in most countries) followed by warfarin. Fibrinolytic therapy has been used successfully in patients with APS [5]. Antiaggregation is commonly used in the first place in patients with arterial events as aPL status is unknown in many cases.

The risk of recurrent thrombosis in patients with APS is high. The level of this risk has been variously reported ranging between 22% to 69% [6–10]. The type of thrombosis is predictive; retrospective analysis of patients with APS and recurrent thrombosis showed that a venous thrombosis is followed by another venous thrombosis in more than 70% of cases, and an arterial thrombosis is followed by another arterial thrombosis in more than 90% of cases [6, 7]. Two recent large and prospective long-term follow-up studies of patients with venous thromboembolism have confirmed that the risk of recurrence in APS patients is significantly higher than in patients without aPL [9, 10]. The cerebral circulation appears to be particularly targeted, with strokes and transient ischemic attacks, movement disorders, epilepsy, myelopathy, and migraine being major manifestations. The rate of recurrent stroke has also been shown to be extremely high in patients with moderate-to-high titers of aCL [11, 12].

Retrospective studies published between 1992–1995 by Rosove et al [6], Derksen et al [13], and Khamashta et al [7] showed the need for prolonged anticoagulation of patients with APS presenting with thrombosis, because the risk of recurrent thrombosis in patients not having, and especially stopping anticoagulation, was unacceptably high – and consistently shown across the studies. Based on these data, indefinite anticoagulation has been accepted by most authors as the standard secondary prophylaxis for thrombosis in patients with APS [14, 15]. It is not clear, however, whether prolonged anticoagulation is necessary in APS patients whose first thrombotic episode developed in association with surgery, oral contraceptive pill, pregnancy, or other circumstantial thrombotic risk factors.

The second relevant finding of the studies by Rosove at al [6] and Khamashta et al [7] was the decreased risk of recurrent thrombosis of patients treated with oral anticoagulation targeted to an international normalized ratio (INR) higher than 3.0 as compared with those aimed to a lower intensity. In addition, low-dose aspirin alone was less effective in preventing recurrent thrombosis than high-intensity anticoagulation. The message from these studies would be to target the intensity of anticoagulation to a higher level than the standard for other conditions such as atrial fibrillation.

Criticism of these studies includes the retrospective design and thus, the nonrandomized assignment of treatment, which is obviously a major limitation. Also, patients with arterial and venous events could not be analysed separately in any of these series due to sample size issues. Furthermore, a number of small subsequent series of patients with venous thromboembolism and aPL found no increased risk of thromboembolic events in patients treated with standard intensity warfarin [9, 10, 16–18]. All the above, together with the fear of increasing hemorrhage as INR rises, made some authors claim a standard 2.0–3.0 anticoagulation target for all patients with APS and thrombosis, irrespective of the vascular bed [19].

Three studies recently published aimed to shed some light on this controversy. In the first, our group analysed a series of 66 patients with definite APS according to Sapporo classification criteria [20] treated with oral anticoagulation to a target INR 3.0–4.0 [21]. The major results of our study were 3-fold: The intensity of anticoagulation was frequently lower than desired, although the INR was very rarely below 2.0; the frequency of life-threatening bleeding was not higher than in patients from other series and treated with lower intensities of anticoagulation, and several APS patients experienced recurrent thrombosis at INRs between 2.0–3.0 (5 documented cases with INRs ranging from 2.1–2.6), most of them having additional risk factors