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Review

Bridging therapy in antiphospholipid syndrome and antiphospholipid antibodies carriers: Case series and review of the literature ☆

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ABSTRACT

Peri-operative management of patients on warfarin involves assessing and balancing individual risks for thromboembolism and bleeding. The timing of warfarin withdrawal and a tailored pre/postoperative management (including the substitution of heparin in place of warfarin, the so-called bridging therapy) is critical in patients with prothrombotic conditions. The antiphospholipid syndrome (APS) is the most common cause of acquired thrombophilia. In this particular subset of patients, as the risk of thrombosis is higher than in general population, bridging therapy can represent a real challenge for treating physicians. Only few studies have been designed to address this topic.

We aim to report our experience and to review the available literature in the peri-procedural management of APS and antiphospholipid antibody-positive patients, reporting adverse events and attempting to identify potential risk factor associated with thrombosis or bleeding complications.

Contents

1. Introduction

Peri-operative management of patients on warfarin involves assessing and balancing individual risks for thromboembolism [1,2] and bleeding [3]. Indeed, the timing of warfarin withdrawal and a tailored pre/postoperative management (the so-called bridging therapy) are critical elements to avoid thromboembolic complications. Bridging therapy is defined as the temporary peri-operative substitution of low-molecular-weight heparin (LMWH) or unfractionated heparin (UH) in place of warfarin [4]. An effective bridging therapy approach aims to both control the thromboembolic risk that drives the need for an aggressive peri-procedural strategy (bridging therapy), and the procedural bleeding risk determines how and when anticoagulant therapy should be resumed [1,5].

Despite several strategies with various clinical indications are nowadays available [5,6], data from randomized controlled trials are still limited and the question of whether patients should undergo bridging therapy is not resolved [1,7].

Recently, Siegel et al. [6] showed an increased bleeding risk in heparin bridged patients compared with non-bridged, whereas the thrombotic

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risk seems not to differ between the two groups [6]. Two prospective randomized trials (PERIOP-2 and BRIDGE) attempting to address this uncertainty are ongoing [8].

All together, due to the lack of sound evidence, an individualized approach and involvement of the patient in decision making process is at present advised [7].

The antiphospholipid syndrome (APS) is the most common cause of acquired thrombophilia [7,9,10], characterized by the association of antiphospholipid antibodies (aPL) with thrombosis and/or pregnancy loss [11]. Thrombotic events can affect venous, arterial side or the microvascular district.

In the presence of aPL, the therapeutic approach is influenced by the presence of previous clinical manifestations [2]. For aPL carriers, without history of vascular and/or obstetric events, thromboprophylaxis in acute high-risk situations is highly recommended. Secondary thromboprophylaxis in APS with thrombosis is provided using oral anticoagulant (OAT), normally lifelong. Therapy in pregnant women with APS aims to improve both maternal and fetal outcomes; APS patients with a history of pregnancy morbidity but no vascular thrombosis are usually treated with prophylactic doses of LMWH plus low-dose aspirin (LDA). Patients with a history of thrombotic events should receive full antithrombotic doses of LMWH plus LDA. For all cases anticoagulation for 6 weeks of postpartum is warranted [11,12].

Bridging therapy in APS patients has been evaluated in only few studies designed to address this topic [13,14]. In this particular subset of patients, as the risk of thrombosis is higher than in general population [15], bridging therapy can represent a real challenge for treating physicians [16].

This case study aimed to report our experience in the periprocedural management in a cohort of APS and aPL-positive patients attending the Immunology Department, reporting adverse events and attempting to identify potential risk factor associated with thrombosis or bleeding complications.

2. Patients and methods

This study retrospectively included 36 consecutive patients undergoing any invasive procedure who attended Immunology Department at Ospedale Umberto I, Torino from April 2005 to June 20013. All patients tested positive at least twice for aPL and 16 of those fulfilled the current APS classification criteria [17]. Demographic, clinical and laboratory characteristics are summarized in Table 1.

Table 1
Demographic and immunological characteristics of the 36 patients treated with bridging therapy.

	APS n. 16	APL n. 20
F/M	13/3	20/0
Age at procedure (years)	49 (31–73)	36 (21–53)
Time of APS/aPL diagnosis	1992–2002	1995–2011
aPL profile		
M I*	12 (triple positivity in 9)	13 (triple positivity in 8)
M IIa	2	3
Other autoimmune diseases associated	68% (56% patients with SLE)	70% (25% patients with SLE)
Procedures time frame	1/2006–1/2013	4/2005–6/2013
Obstetrical intervention	47%	84,6%
Thrombotic adverse events	2 venous, 1 arterial	1 venous
Hemorragic adverse events	1	0

* M I, aPL profile according to Myiakis I [17]: more than one laboratory criteria present (any combination); M IIa, profile according to Myiakis Iia [17]: LA present alone; Triple positivity: LA, aCL, anti-b2glycoprotein-I antibodies.

Inclusion criteria for this study were (1) confirmed aPL positivity, (2) antiaggregant or OAT because of clinical history of thrombosis and/or pregnancy morbidity and (3) bridging therapy required for invasive procedure. Included patients met all the above inclusion criteria.

Thrombotic risks assessment included arterial hypertension (systolic pressure > 140 mm Hg or diastolic pressure > 90 mm Hg), obesity (body mass index > 30 kg/m^2), diabetes mellitus (baseline glycemia > 126 mg/dl in at least two occasions), smoking, active or treated neoplasia, use of oral contraceptives, underlying systemic autoimmune diseases and genetic hypercoagulables states.

The considered bleeding risks factors were previous hemorrhagic events, thrombocytopenia, use of non-steroidal anti-inflammatory drugs (NSAIDs), von Willebrand disease and coagulation factors deficiencies [18].

Preoperative therapy, time of stopping and LMWH doses before and after intervention were retrospectively collected. Adverse events, namely, thrombosis and bleeding, were as previously defined [18].

3. Autoantibodies detection

The aCL and the anti-β2GPI were detected by ELISA as described previously [19]. Plasma samples were tested for the presence of LA according to the recommended criteria from the ISTH Subcommittee on lupus anticoagulant-phospholipid-dependent antibodies [20].

4. Results

We retrospectively described 45 procedures in 36 aPL-positive patients: of those, 20 (55%) were aPL carriers and 16 (44%) were APS. Demographic and immunological characteristics are reported in Table 1. Overall, we described one hemorrhagic and four thrombotic events. Three thrombotic events occurred in the APS group (2 venous and 1 arterial thrombosis), while 1 venous thrombosis occurred in the aPL carrier group.

Tables 2 and 3 summarized the outcomes in all APS and aPL patients, respectively.

A detailed case analysis is reported in Table 4. A case-by-case analysis of patients who suffered for any adverse outcome has been performed, as follows:

Event 1 (patient 8): a patient with obstetric APS developed deep vein thrombosis (DVT) in the postpartum period because of fixed dose of LMWH (enoxaparin 40 mg, equivalent to 4000 IU; with weight 80 kg corresponding to 50 U/kg/die).

Event 2 (patient 17): an aPL-positive patient with undifferentiated connective tissue disease (UCTD) developed a cerebral venous thrombosis (CVT) after labor, which occurred 66 hours after LMWH was stopped. Concomitant microcytic anemia (Hb 7,8) favored the adverse event.

Event 3 (patient 15): a patient with thrombotic APS (DVT) in SLE (malar rash, photosensivity, arthritis, anti-nuclear antibodies, anti-DNA antibodies), who was on LDA because she stopped OAT few years ago, developed DVT after necrosectomy of necrotic ulcer tissue followed by skin graft. She received LMWH (enoxiparin 40 mg OD) for 8 days. Smoke and bed rest, added to low dosage and short period of heparin prophylaxis could justify the onset of DVT.

Event 4 (patient 14): a patient with thrombotic APS (pulmonary embolism) in SLE (autoimmune hemolytic anemia, arthritis, sierositis and anti-nuclear antibodies), presented hemorrhage (loss of 6 g Hb) followed by thrombotic event (myocardial infarction) after orthopedic procedure. NSAIDs post-surgery prescription and early somministration of LMWH could explain significant bleeding, whereas smoke, post-splenectomy thrombocytosis were highlighted as arterial