PB3.62 – Antiphospholipid- IV

PB 3.62-1
Antiphospholipid syndrome in children
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Background: Antiphospholipid Syndrome (APS) is more frequent in adults than in children. Cohort studies estimate up to 7% of children with venous thromboembolism (VTE) may meet criteria for APS; however, pediatric studies are lacking.

Aims: To describe a large cohort of childhood APS, examining laboratory and clinical characteristics.

Methods: A retrospective cohort from the Hospital for Sick Children (Toronto) included patients <18 years of age diagnosed between 1999 and 2011. Patients were identified from the pediatric thrombosis/thrombophilia databases. Only patients meeting revised Sapporo criteria were included. Demographic, laboratory and clinical data were extracted from medical records. Thrombus resolution for multiple initial thrombi was defined as complete resolution of ≥50% of thrombi. Complete thrombophilia evaluation included factor V Leiden (FVL), prothrombin variant, deficiencies in protein C/S and antithrombin testing. Patients with primary vs. secondary APS were compared using descriptive, parametric and nonparametric statistics as appropriate. Study was approved and consent waived by the local research ethics board.

Results: Over the 12-year study period, 53 patients were identified. Seventy-five percent of the cohort had secondary APS (systemic lupus erythematosus [33%], others [67%]). The overall cohort median age was 11 years (IQR: 1–14; M:F 1:4; 94±10). There were 57% venous, 34% arterial and 9% mixed thrombi, distributed as follows: central nervous system (CNS) (38%); non-CNS (49%); and both (13%). APS laboratory criteria consisted of persistent elevation in anticardiolipin IgG antibodies (75%) and persistent positive lupus anticoagulant (55%). Complete thrombophilia evaluation was done in 44/53 (83%) patients, partial in 6/53 (11%), and missing in three patients. Overall, 36/53 (68%) patients had no concomitant thrombophilia, 9% had incomplete evaluation but showed no defects, and 17% had a positive finding, as follows: FVL (homozygous [1], heterozygous [5]), prothrombin variant [heterozygous (1)], protein S deficiency (1), none with combined defects. Eighty-nine percent of children received some duration of anticoagulation. On follow-up imaging 64% had no/incomplete radiological resolution, 34% had complete resolution, and 2% had progression. At least one clinical recurrence occurred in 7/53 (13%) patients. There was no statistically significant difference in sex, thrombus type/location, thrombophilia status, resolution or recurrence in children with primary vs. secondary APS. There was however a significant difference in proportion of children ≤10 vs. >10 years of age in primary vs. secondary APS groups (P = 0.005). There was no statistically significant difference in clinical recurrence based on thrombophilia status nor treatment status, 6/7 recurrences occurred in patients with a negative complete thrombophilia evaluation. At the time of recurrence only 1/7 was therapeutic in their anticoagulation.

Summary/Conclusion: Diagnostically proven APS is rare in children, with secondary APS being seen more frequently. Younger children more frequently had secondary APS, while older children had a more even distribution of primary and secondary cases. Clinical recurrence was low in this cohort, particularly considering the concomitant thrombophilia rate described, and recurrence was not associated with thrombophilia status. Interestingly, most children within this cohort received some duration of anticoagulation and recurrence occurred mostly during subtherapeutic anticoagulation levels. Further prospective work is necessary to explore the ideal anticoagulation length in this population.

PB 3.62-2
RAPS: a prospective randomised controlled phase II/III clinical trial of rivaroxaban vs. warfarin in patients with thrombotic antiphospholipid syndrome, with or without SLE
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Background: The current mainstream of the treatment of thrombotic antiphospholipid syndrome (APS) is therapeutic anticoagulation with vitamin K antagonists (VKA), such as warfarin. However, the limitations of VKA have driven a search for new agents, which include riva-roxaban (Xarelto®; Bayer HealthCare). These drugs have been approved for several clinical indications at present based on phase III prospective randomised clinical trials, but these trials may not be directly applicable to patients with APS where there remains an unmet need.

Aim: To demonstrate that the intensity of anticoagulation achieved with rivaroxaban is not inferior to that of warfarin, by measurement of the dynamics of ex vivo thrombin generation using the thrombin generation test (TGT) with the endogenous thrombin potential (ETP) as the key parameter, in patients with thrombotic APS, with or without SLE. Secondary aims: to compare rates of bleeding and recurrent thrombosis, and compare quality of life in patients on rivaroxaban with those on warfarin.

Hypothesis: The intensity of anticoagulation, assessed using the ETP, achieved in thrombotic APS patients on rivaroxaban is not inferior to that obtained on warfarin. The TGT, as a global measure of anticoagulation, can assess the anticoagulant effects of both rivaroxaban and warfarin. Clinically, our hypothesis is that in patients with thrombotic APS, rivaroxaban could induce more predictable anticoagulation and, therefore, a greater sustained reduction in thrombin generation than would warfarin, with additional patient benefits because there is no requirement for regular anticoagulation monitoring.

Methods: 156 eligible patients with thrombotic APS, with or without SLE, who have had either a single episode of VTE whilst not on anticoagulation or recurrent episode(s) which occurred whilst off anticoagulation or on sub-therapeutic anticoagulant therapy, currently taking warfarin, target INR 2.5 (range 2.0–3.0), will be randomised either to continue warfarin (standard of care) or to stop warfarin and start riva-roxaban 20 mg once daily as standard. Each patient will have a 6 month treatment period and a final visit 30 days after the end of trial treatment. The planned recruitment period is 10 months and overall trial duration is 24 months.

Results: The primary outcome measure is the percentage change in ETP from randomisation to day 42. The differences between the two arms for the quality of life, efficacy (venous thromboembolism and other thrombotic events) and safety (serious adverse events and all bleeding events) secondary outcomes will be presented as estimates and 95% confidence intervals.

Conclusion: If the trial demonstrates: i) that the anticoagulant effect of rivaroxaban is not inferior to that of warfarin using the ETP; and ii) absence of any adverse effects that cause concern with regard to the use of rivaroxaban, we believe that this would provide sufficient supporting information to change practice for our patients, i.e. to make rivaroxaban the standard of care for the treatment of patients with thrombotic APS, with or without SLE.