CLINICAL VIGNETTE

Anticoagulation in the Setting of the Antiphospholipid Syndrome

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Case Presentation

A 56-year-old female with migraines and hyperlipidemia presented to the emergency room with subacute headaches and impaired speech. She reported intermittent headaches different from her prior migraines for the last 4-6 weeks as well as several days of impaired speech with mild word-finding difficulty. She had been evaluated several weeks prior with a reported negative CT brain at that time. Her physical exam at presentation was notable for mild word hesitancy, but overall fluent speech. Brain MRI revealed subacute punctate infarcts in the right frontoparietal lobe. Based on the MRI, suspected etiology of her subacute CVAs was embolic. Further evaluation including telemetry and echocardiogram were unrevealing, but labs were remarkable for an elevated dilute Russel viper venom time (DRVVT), elevated beta-2-glycoprotein IgG of 97, and cardiolipin IgG of 76 consistent with hypercoagulable state due to anti phospholipid syndrome (APS). She was discharged on rivaroxaban 20 mg qhs, but returned to ER 5 days after discharge with acute right facial droop and slurred speech. Repeat Brain MRI showed multiple, new, small ischemic infarcts in multiple vascular territories. She was subsequently switched to unfractionated heparin, transitioned to warfarin, and discharged when INR was at goal with close rheumatology and hematology follow-up.

Discussion

The antiphosphlipid syndrome is a "systemic autoimmune disease defined by thrombotic or obstetrics events that occur in patients with persistent antiphospholipid antibodies."[1] This syndrome often occurs in conjunction with other autoimmune diseases, but may occur in the absence of another autoimmune disorder, otherwise known as primary antiphospholipid syndrome. The revised Sapporo criteria (also known as the Sydney criteria) are used to diagnose and classify APS. These define APS if at least 1 clinical criteria (thrombosis or pregnancy morbidity) and 1 laboratory criteria are present.[2] Lab criteria include lupus anticoagulant, anticardioliipin or anti-beta-2 glycoprotein-I at or above specified levels on 2 occasions at least 12 weeks apart. In the setting of acute thrombosis, the diagnosis of APS cannot be confirmed by these criteria until repeat testing at least 12 weeks after the initial event. Furthermore, additional antibodies and clinical features common in APS are not included in the diagnostic criteria.

The primary driver of the prothrombotic state in APS is binding of antibodies to beta-2 glycoprotein-I leading to inflammation and thrombosis. However, the risk of thrombosis is multifactorial, and the risk of a new event in a patient with antiphospholipid antibodies without other risk factors is estimated to be <1% per year.[1] When additional risk factors are present, risk may increase substantially. Once a thrombotic even has occurred, the general recommendation is to initially treat with heparin and then transition to a vitamin K antagonist such as warfarin. Unfortunately, recurrent thrombotic events can occur even at therapeutic INR on warfarin. Over the last several years, direct oral anticoagulants (DOACs) have been approved for treatment and prevention of venous thrombosis as well as stroke prevention in setting of atrial fibrillation as they have been found to be non-inferior compared to warfarin or heparin. They provide potential quality of life improvement and improved medication adherence which has led investigations to wonder if they can be used in other clinical scenarios such as APS.

The Rivaroxaban in Antiphospholipid Syndrome (RAPS) trial was the first randomized control trial on DOAC use in APS patients.[3] However, this trial was not designed to assess for clinical non-inferiority, but instead assessed laboratory values comparing thrombin generation and potential thrombotic risk between warfarin treatment and rivaroxaban treatment, and concluded they were similar. These encouraging results set the stage for the Rivaroxaban in Thrombotic Antiphospholipid Syndrome (TRAPS) trial which was designed to assess for non-inferiority between rivaroxaban and warfarin in this patient population. It started in November 2014 with a goal to recruit 536 patients, but was stopped early in January 2018 after enrolling only 120 patients due to an increased major event rate in the rivaroxaban group compared to the warfarin group - there were 11 significant events in the rivaroxban group (4 ischemic CVAs, 3 MIs, and 4 major bleeds) versus 2 in the warfarin group (0 ischemic CVA, 0 MI, and 2 major bleeds).[4] Based on these results, rivaroxaban seems to be inadequate for APS, but further testing of the DOACs in general for APS is ongoing with ASTRO-APS currently studying the utility of apixaban.[5,6]

Conclusion

While DOACs have many uses and advantages over warfarin for certain indications, the evidence has been very limited for their use in the setting of APS. Although ongoing studies such as ASTRO-APS may yet yield better information, with rivaroxaban's failure in the TRAPS trial earlier this year, warfarin should still be the default anticoagulant in this high risk patient

population. If a DOAC is desired in this situation, guidance from a hematologist should help facilitate discussion of the risks and benefits of this management choice with the patient. Finally, this case illustrates that different anticoagulation treatments are not equivalent and understanding the specific indication for anticoagulation is key in choosing the best treatment choice.

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Submitted November 21, 2018