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THU0213 TRAASVIR STUDY: THROMBOTIC MANIFESTATIONS IN ANTIPHOSPHOLIPID ANTIBODY TRANSIENT POSITIVITY RELATED TO VIRAL INFECTIONS:

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Background: The molecular pathogenesis of antiphospholipid syndrome is complex (environmental triggers, predisposed individuals). Previous studies suggested that infection may lead to the development of transiently elevated non-thrombogenic aPL antibodies. However, there are increasing case reports of patients with viral infections who develop antiphospholipid antibodies and thromboembolic events.

Objectives: To evaluate the role of acute viral infections in the development of thrombotic events related to aPL transitory (or permanent) positivity.

Methods: We include patients with a current viral infection that was diagnosed before elevated aPL antibodies were identified. One positive laboratory test either LA, aCL, or anti β 2 GPI antibodies after a prior diagnosis of infection was required (< 3 months). Infection must be followed by thromboembolic manifestations (arterial or venous). A time frame of 3 months between infection diagnosis and recognition of aPL antibodies positivity was established. Normal PT and APTT test were observed in all previous patient's blood tests.

Results: From January 2014 to date we have collected 40 cases with a demonstrated acute virosis and an aPL positive result with a thrombotic manifestation. 9 cases (22.5%) for Epstein-Barr virus, 17 cases (42.5%) were positive for CMV, 8 (20%) for Parvovirus B19, 3 cases were positive for Influenza A H1N1,3 for HIV, 1 for RSV, 1 for HCV and 1 case for Rotavirus. Lupus anticoagulant (L A) positivity was showed in 22 cases (55%), 15 cases (37.5%) tested positive for IgM anticardiolipin antibody and 13 cases (32.5%) also tested positive for IgM anti- β 2GPI antibodies. Unfortunately, anti-prothrombin antibodies could not be analysed. The clinical manifestations were: leg deep venous thrombosis (17 cases) (42.5%), pulmonary embolism (5 cases) (12.5%), superior limbs (3 cases) (7.5%) livedoid vasculopathy (3 cases) (7.5%), splenic

infarction (1 case), ovarian venous thrombosis (1 case). Only four arterial thromboses were observed: superior limbs (2 cases), digital ischemia (1 case) and transverse myelitis (1 case). We have observed how the IgM virus related antibody became negative and the aPL became negative in parallel in 20/40 cases (50%).

Conclusion: We hypothesized that thrombotic manifestations of aPL-related acute viral infections are underdiagnosed, and probably in predisposed host, some viral infections may induce the transient apparition of aPL, mainly those with LA activity with potential pathogenic thrombotic properties.

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THU0214 THE PI3K δ SELECTIVE INHIBITOR INCB050465 ABROGATES KIDNEY PATHOLOGY IN A SPONTANEOUS MURINE MODEL OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple organs, including the skin, joints and kidneys. Though SLE typically cycles through periods of flares and remission, patients often eventually succumb to end-stage kidney or cardiovascular damage¹. SLE is characterized by the presence of autoantibodies that form immune complexes resulting in kidney deposition that significantly contribute to lupus nephritis pathogenesis. Phosphatidylinositol 3-kinases (PI3Ks) are divided into three classes (Class I, II, and III) according to their structure, regulation and substrate specificity. The Class I PI3K delta isoform (PI3K δ) has been implicated in autoimmune diseases associated with aberrant B cell and antibody responses. INCB050465 is an oral small molecule PI3K δ selective inhibitor currently being evaluated in clinical trials for the inflammatory indications Sjögren's syndrome and autoimmune hemolytic anaemia (NCT03627065 & NCT03538041).

Objectives: To quantify the efficacious potential of INCB050465, a selective PI3K δ inhibitor, in a preclinical model of systemic lupus erythematosus with kidney pathology.

Methods: The MRL/lpr mouse model spontaneously develops multiple inflammatory phenotypes that mimic human SLE pathologies, including kidney damage resulting in proteinuria, cutaneous skin lesions and anti-double stranded DNA (anti-dsDNA) antibodies. Kidney sections were stained with hematoxylin and eosin (H&E) and assigned a composite score based on glomerulus, crescents, protein casts, interstitial inflammation and vasculitis by a rater unaware of the treatment groups². Flow cytometry was performed on splenocytes to characterize B cell and T cell subsets. Anti-dsDNA antibodies were determined by commercial ELISA.

Results: In vitro enzymatic selectivity screening revealed INCB050465 potentially inhibited the PI3K δ kinase enzyme (IC₅₀ = 1.1 $\pm$ 0.5 nM), with 20,000-fold selectivity for the other PI3K family member enzymes. Proteinuria identified spontaneous kidney damage in 85%+ of vehicle treated mice by 21 weeks of age, and kidney histology revealed gross tissue enlargement associated with structural abnormalities. In contrast, therapeutic INCB050465 treatment (0.3 – 3.0 mg/kg, b.i.d.) dose-dependently reduced the incidence of proteinuria (p < 0.01), and kidney structural integrity was normalized (p < 0.0001). A feature of the MRL/lpr model is lymphocyte hyper-proliferation resulting in lymphadenopathy and splenomegaly. Therapeutic INCB050465 treatment dose-dependently reduced spleen (p < 0.01) and lymph node (p < 0.01) weight. Cutaneous skin lesions were unaffected by INCB050465 treatment. Splenocyte flow cytometry revealed no reduction in absolute lymphocyte, CD19⁺ B cell, CD4⁺ or CD8⁺ T cell frequencies following INCB050465 treatment. However