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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

INCB050465 reduced the absolute counts of germinal center (CD19⁺GL7⁺) and marginal zone (CD19⁺CD21⁺) B cell subsets. Anti-dsDNA antibodies were abrogated by INCB050465 therapy ($p < 0.0001$).

Conclusion: INCB050465, a selective PI3K δ inhibitor, was highly efficacious against immune-mediated mechanisms associated with lupus nephritis, but not cutaneous lupus disease manifestations in this preclinical model. Treatment-induced preservation of kidney tissue integrity corresponded to specific B cell subset modulation and autoantibody reduction. Selective PI3K δ inhibitor treatment did not induce lymphocyte depletion.

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THU0215 IGM ANTIBODIES AGAINST MALONDIALDEHYDE AND PHOSPHORYLCHOLINE IN DIFFERENT SYSTEMIC RHEUMATIC DISEASES

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Background: IgM antibodies against phosphorylcholine (anti-PC) and malondialdehyde (anti-MDA) may have protective properties in cardiovascular or rheumatic diseases including SLE and RA.¹⁻⁴ Little is known about their role in other systemic rheumatic conditions.

Objectives: The objective is to compare different rheumatic conditions in relation to these antibodies, and also clinical outcome, with focus on cardiovascular disease. We also aim to characterize them and compare them by use of proteomics.

Methods: IgM anti-PC and anti-MDA was measured using ELISA in patients with SLE (374), RA (354), Mixed connective tissue disease (MCTD, 77), Systemic sclerosis (SSc, 331), Sjögren's syndrome (SjS, 324), primary antiphospholipid syndrome (PAPS, 65), undifferentiated connective tissue disease (UCTD, 118) and 515 matched healthy controls (HC). Cardiovascular score (CV) was broadly defined based on clinical disease symptoms. Anti-PC and anti-MDA peptide/protein characterization were compared using a proteomics de novo sequencing approach. IgM anti-MDA and anti-PC were extracted from total IgM. The proportion of Treg cells was determined by flow cytometry.

Results: The maximal difference between cases and controls was shown for MCTD: significantly lower IgM Anti-PC but not anti-MDA among patients (median 49.3RU/ml vs 70.4 in healthy controls, $p(t\text{-test})=0.0037$). Low levels (below 25th percentile) of anti-PC but not anti-MDA were significantly more prevalent in MCTD, SLE, SjS and SSc. The IgM anti-PC variable region profiles were distinctly different and also more homologous in their content than anti-MDA. Anti-PC but not anti-MDA were significantly negatively correlated with CV in the whole patient group. In contrast to IgM anti-PC, IgM anti-MDA did not promote polarization of Tregs.

Conclusion: Anti-PC could be a protection marker for MCTD and also for SLE, SjS and SSc while anti-MDA did not differ. anti-PC level is negatively correlated with CV in the patient group cohort. These findings could have both diagnostic and therapeutic implications, one possibility being active or passive immunization with PC.

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THU0216 IGG1 ANTIBODIES AGAINST PHOSPHORYLCHOLINE ARE ASSOCIATED WITH PROTECTION IN SLE AND ATHEROSCLEROSIS: POTENTIAL UNDERLYING MECHANISMS

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Background: IgM antibodies against phosphorylcholine (anti-PC) may be protective in atherosclerosis, cardiovascular disease (CVD) and systemic lupus erythematosus (SLE). Less is known about other anti-PC isotypes and subclasses. In this study, we study the role of IgG1 and IgG2 anti-PC, with focus on atherosclerosis and SLE.

Objectives: To study the role of IgG1 and IgG2 anti-PC, with focus on atherosclerosis and SLE, both in a clinical setting and by experimental studies, where we use our in-house produced monoclonal IgG1 anti-PC.

Methods: We determined IgG1 and IgG2 anti-PC in our SLE cohort study (SLEVIC), among 116 SLE-patients from Karolinska University Hospital Huddinge and 110 population controls matched for age and gender. The level of antibodies was measured by ELISA. For functional studies, we used three of our in-house generated, fully human monoclonal IgG1 anti-PC (A01, D05, E01). Primary human macrophages were derived from peripheral blood. Apoptosis was induced in Jurkat T-cells and pre-incubated with A01, D05, E01 or isotype control IgG1 and effect on phagocytosis by macrophages studied. Anti-PC peptide/protein characterization was determined in anti-PC clones compared to isotype control using a proteomics de novo sequencing approach.

Results: IgG1 but not IgG2 anti-PC levels were higher among SLE patients than controls ($p=0.02$). IgG1 anti-PC was negatively associated with prevalence of atherosclerotic plaques, below 10th percentile, (OR: 2.48, CI: 0.69-9.00). IgG1 Anti-PC was negatively associated with CVD, SLICC and SLEDAI (OR: 4.74 CI: 1.29-17.39, OR: 2.978 CI: 0.876-10.098, OR: 5.108 CI 1.3 20.067 respectively). Monoclonal D05 had maximum effect on macrophage efferocytosis efficiency, followed by A01 and E01. This is because anti-PC IgG1s bind to phosphorylcholine exposed on apoptotic cells and facilitate the uptake by macrophage. The in-house produced monoclonal antibodies showed differential binding specificity to PC and PC associated neo-epitopes. Peptide analysis showed difference in the CDR3 region of the three anti-PC IgG1 clones which are crucial for recognition of the phosphorylcholine on the apoptotic cell surface and other neo-epitopes.