1 REPOSITORY CORTICOTROPIN INJECTION (H.P. ACTHAR GEL) REVERSES CRITICAL ELEMENTS OF THE TLR9/ANTI-IGM RESPONSE IN HUMAN B CELLS IN VITRO

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Background Signaling through Toll-Like Receptor 9 (TLR9) is a central event in the activation of normal B cells and in the production of pathogenic autoantibodies in diseases such as systemic lupus erythematosus (SLE). We sought evidence for direct effects of repository corticotropin injection (RCI; H.P. Acthar Gel), an FDA-approved treatment for selected cases of SLE, on isolated human B lymphocytes activated *in vitro* by engagement of TLR9 and the B cell receptor.

Methods CD19⁺ B cells from healthy volunteers (n=3) were activated *in vitro* with the TLR9 ligand ODN 2395 and anti-IgM. RCI was added to cultures at concentrations over a 20-fold range (controls received equal volumes of placebo gel). Messenger RNA was isolated from cells after one day in culture and cDNA libraries were prepared for multiplexed high-throughput sequencing on an Illumina HiSeq 2500. Analyses of RNA-Seq reads utilized Illumina CASAVA pipeline Version 1.8. RUVSeq R package v3.1 and edgeR were used to identify differentially expressed genes in paired comparisons between unstimulated and TLR9/anti-IgM activated cells and between activated cells treated with RCI and placebo.

Results Treatment of B cells in steroid-free medium with ODN 2395/anti-IgM resulted in significant, reproducible induction of 162 distinct mRNAs (mean induction=8.87 ± 0.95 fold; range=2.5–118.3-fold) and suppression of 80 mRNAs (mean suppression to 21.8% ± 0.8% of baseline; range=6% to 39% of baseline) at 24 hours. RCI treatment resulted in significant, reproducible suppression of 14 of the ODN 2395/IgM-induced mRNAs (mean suppression to 23.6% ± 3.1% of stimulated value; range 9.9% to 41.2%). The RCI-suppressed mRNAs included two key regulators of class switch recombination, AICDA and BATF. RCI treatment also resulted in significant, reproducible induction of 5 of the ODN 2395/IgM-suppressed mRNAs (mean induction by RCI=7.65 ± 2.34 fold;

range=4.7 to 16.9-fold). The RCI-induced mRNAs included SLAM family member Ly9 (SLAMF3), a cell surface receptor capable of inhibiting autoantibody responses. No ODN 2395/IgM-induced mRNAs were further increased after RCI treatment and no ODN 2395/IgM-suppressed mRNAs were further reduced after RCI treatment (p=0.0002; Fishers exact test).

Conclusions RCI treatment of human B cells cultured under steroid-free conditions and activated with TLR9 agonist ligand and B cell receptor stimulation resulted in reversal of elements of the early mRNA activation response, including two key regulators of somatic hypermutation, AICDA and BATF. Whether these effects are related to clinical actions of RCI in SLE will be of interest for future investigation.

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2 A SIMPLIFIED RISK STRATIFICATION MODEL EFFECTIVELY PREDICT THE PROGNOSIS OF CHINESE PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONNECTIVE TISSUE DISEASE

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Background To verify the prognostic value of simplified risk assessment strategy based on 2015 European pulmonary hypertension (PH) guidelines at baseline and long-term follow-up in Chinese connective tissue disease (CTD) associated pulmonary arterial hypertension (PAH) patients.

Methods This single-center retrospective study included 50 patients with right heart catheterization (RHC) diagnosed PAH accompanied by systemic lupus erythematosus (SLE), primary Sjogrens syndrome (pSS), mixed CTD (MCTD) or systemic sclerosis (SSc) who hospitalized in the first affiliated hospital of Nanjing Medical University from April 2009 to May 2018. The data of demographics, symptoms, WHO functional class, 6 min walking distance (6MWD), blood biochemistry, transthoracic echocardiography, high-resolution computer tomography, RHC and treatment was collected at the baseline and follow-up visit. The risk

Abstract 2 Table 1 Included variables and cut-off values used for simplified risk assessment instrument

Variables	Low risk	Intermediate risk	High risk
WHO Functional Class	I-II	III	IV
6MWD	>440 m	165–440 m	<165 m
NT-proBNP plasma levels	<300 ng/L	300–1400 ng/L	>1400 ng/L
Imaging (echocardiography)	No pericardial effusion	No or minimal pericardial effusion	Pericardial effusion
Haemodynamics	right atrial pressure<8 mmHg cardiac index≥2.5 L/min/m ² SvO ₂ >65%	right atrial pressure 8–14 mmHg cardiac index 2.0–2.4 L/min/m ² SvO ₂ 60%–65%	right atrial pressure>14 mmHg cardiac index<2.0 L/min/m ² SvO ₂ <60%

6MWD: 6 min walk distance; NT-proBNP: N-terminal pro-B-type natriuretic peptide; SvO₂: mixed venous oxygen saturation.