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.

Funding Source(s): Mallinckrodt Pharmaceuticals

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

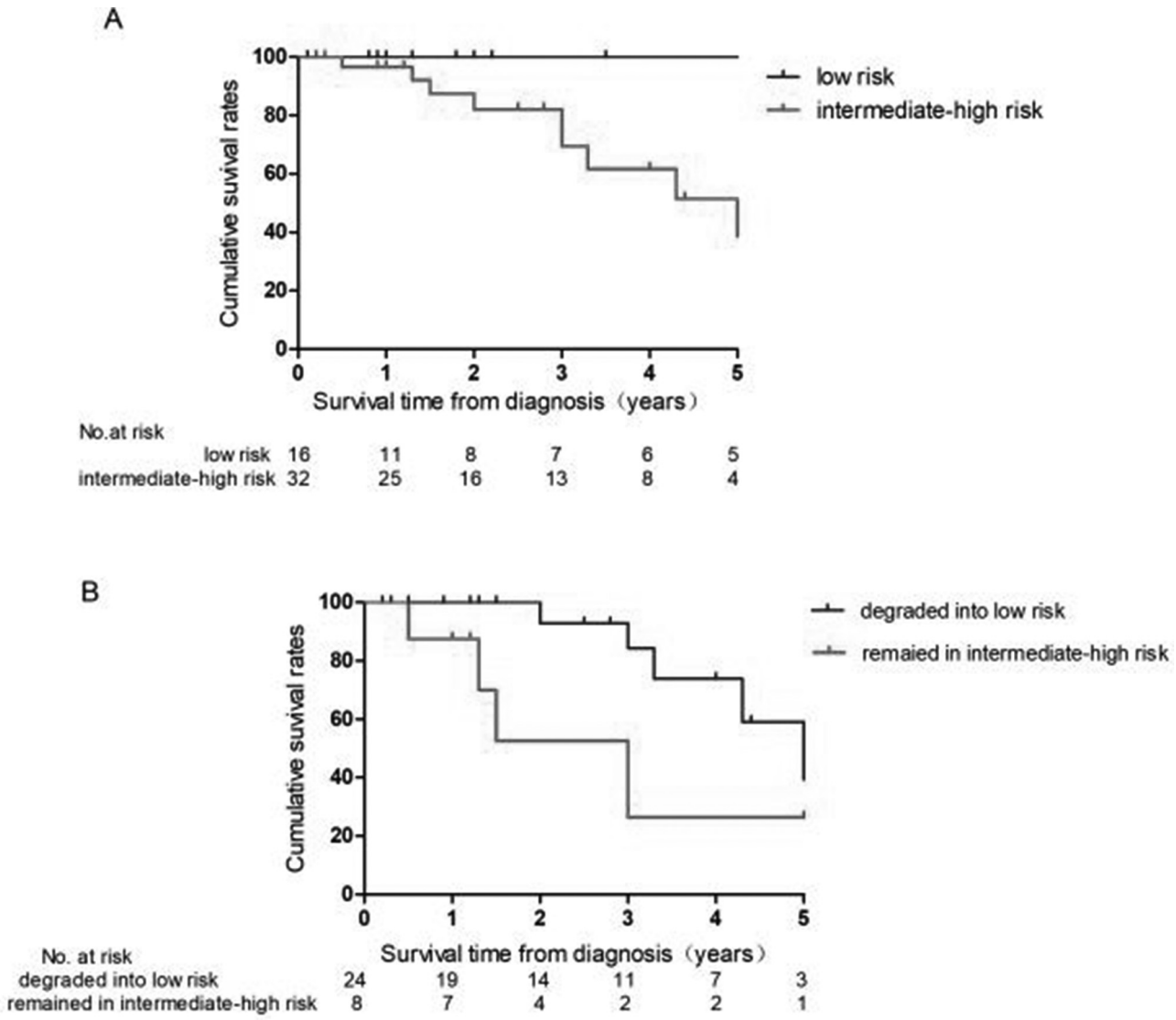
Abstract 2 Table 1 Included variables and cut-off values used for simplified risk assessment instrument

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/m2 SvO2>65%	right atrial pressure 8–14 mmHg cardiac index 2.0–2.4 L/min/m2 SvO2 60%–65%	right atrial pressure>14 mmHg cardiac index<2.0 L/min/m2 SvO2<60%

6MWD: 6 min walk distance; NT-proBNP: N-terminal pro-B-type natriuretic peptide; SvO_2: mixed venous oxygen saturation.

Abstract 2 Table 2 Characteristics of the patients included in the baseline risk grade group.

Characteristic	All patients	Low Risk	Intermediate-High Risk	P value
Patients, n	50	16	34	-----
Female, n(%)	47(94%)	15(94%)	32(94%)	0.9593
Age, years	39.12±1.90	40.19±3.25	38.62±2.37	0.7046
Duration from diagnosis of CTD to diagnosis of PAH, months	36.49±10.36	77.43±29.94	21.88±9.09	0.0874
Duration from symptoms onset to diagnosis of PAH, months	16.22±3.82	14.09±3.11	13.79±3.18	0.4502
Onset with PAH, (n%)	12(24%)	3(19%)	8(24%)	0.7035
Underlying CTD				
SLE, n(%)	22(44%)	6(38%)	16(47%)	0.5253
pSS, n(%)	14(28%)	5(31%)	9(26%)	0.7255
SSc, n(%)	5(10%)	2(13%)	3(9%)	0.6498
UCTD, n(%)	4(8%)	1(6%)	3(9%)	1.0000
MCTD, n(%)	5(10%)	2(13%)	3(9%)	0.6498
pericardial effusion, n%	15(30%)	1(6%)	14(41%)	**0.0186**
RHC parameters				
right atrial pressure, mmHg	7.04±0.77	4.33±0.77	8.31±1.00	**0.0141**
mPAP, mmHg	45.60±1.57	39.13±1.70	48.62±1.97	**0.0036**
PAWP, mmHg	8.74±0.54	8.88±0/98	8.68±0.65	0.8969
PVR, Wood unit	10.63±1.37	5.78±0.71	13.06±1.84	**0.0108**
cardiac index, L/min/m2	2.74±0.19	3.64±0.35	2.29±0.18	**0.0005**
SvO2, %	61.47±1.70	69.80±1.42	57.68±1.90	**0.0003**
6MWD, m	369.8±31.91	438.9±23.41	351.6±26.23	**0.0250**
WHO Functional Class				
I-II,n%	18(36%)	3(19%)	5(15%)	0.6994
III-IV,n%	32(64%)	13(81%)	29(85%)	-----
NT-pro-BNP, ng/L	1790±393.1	262.9±90.08	2515±556.9	**<0.0001**
Uric acid, umol/L	364.8±17.04	325.9±27.30	383.1±21.05	0.1731
IgG, g/L	16.93±1.03	19.52±1.56	15.7±1.28	0.0506
mild ILD, n(%	25(50%)	9(56%)	18(53%)	0.8327
Treatment				
Glucocorticoid,n(%)	46(92%)	15(94%)	31(91%)	0.7544
Immunosuppressant,n(%)	38(76%)	13(81%)	25(74%)	0.5510
PAH-Targeted therapy				
none,n(%)	4(8%)	1(6%)	3(9%)	1.0000
PDE5I ,n(%)	17(34%)	7(44%)	9(26%)	-----
ERA,n(%)	13(26%)	4(25%)	9(26%)	-----
ERA+PDE5I,n(%)	16(32%)	4(25%)	11(32%)	-----
mean treatment duration, months	17.57±2.98	19.13±6.23	16.48±3.27	0.9811



Abstract 2 Figure 1 (A) five-year survival rate based on baseline risk stratification. The estimated survival was differed between low risk group and intermediate-high risk group (p=0.019); (B) three-year survival rate of CTD-PAH patients based on follow-up risk assessment. Patients who remained in intermediate-high risk group after treatment initiation have poorer outcome

stratification was performed according to the 2015 European PH guidelines. WHO functional class, 6MWD, N-terminal pro-B-type natriuretic peptide (NT-proBNP), pericardial effusion, right atrial pressure, cardiac index and mixed venous oxygen saturation (SvO2) were the mainly variables to calculate the risk grade. Survival rate was analysed by the Kapla-Meier method and differences between groups were assessed by Long-Rank test.

Results In this study, SLE-PAH was the most common CTD-PAH (44%), followed by pSS-PAH (28%). We divided all patients into two groups (low risk and intermediate-high risk group) according to the risk stratification. The change of risk stratification during follow-up visits was evaluated. Intermediate-high risk group at baseline exhibited a poorer long-term outcome than low risk group (p=0.0098), the 1-, 3- and 5 year survival rate were 97%, 69% and 39%, respectively. While no patient was died in low risk group. 24 patients in intermediate-high risk group were degraded into low risk group during the follow-up visit. The estimated 1-, 3- and 5 year survival rate were 100%, 84% and 39% for patients who degraded from intermediate-high risk group to low risk group while 88%, 26% and 26% for patients who remained in intermediate-high risk group.

Conclusions The simplified risk stratification model based on 2015 European PH guidelines effectively identified the prognosis of Chinese CTD-PAH patients. Patients have a reduced mortality risk in low risk grade at baseline and stable in low risk grade after long-term treatment.

Funding Source(s): Kaplan-Meier analysis of survival in different risk group patients at baseline and follow-up visit.