30 ASSOCIATION AND FUNCTIONAL STUDIES OF GENETIC POLYMORPHISMS OF MFG-E8 GENE IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by impaired clearance of apoptotic cells. Milk fat globule epidermal growth factor8 (MFG-E8) is a protein connects between v3 integrin of phagocytic macrophage and phosphatidylserine of apoptotic cell surface. In this study, we determine whether genetic variation of MFG-E8 gene and serum protein concentration are associated with SLE.

Methods Single nucleotide polymorphisms (SNPs) were genotyped by three steps. At first, we used polymerase chain reaction in 20 patients with SLE and 20 normal controls (NC) for sequencing of a whole MFG-E8 gene in Korean population. Then we screened 12 selected SNPs in 55 SLE and 30 NC. Finally, we used Taq-man probe assay in 225 SLE and 230 NC for genotyping of targeted 5 SNPs. Furthermore, serum MFG-E8 concentrations were analysed in SLE.

Results SLE patient's mean age was 35.7±7.8 years and 92% were women, which is not different form NC. rs2271715's C allele and rs3743388's G allele were shown higher frequency in SLE than NC (p=0.036, p=0.005, respectively). As the linkage disequilibrium test, rs1878326 and rs1878327 were shown high linkage (r^2=0.879). Three haplotypes were found by four SNPs (rs4945, rs1878327, rs2271715, and rs3743388); AACG, CGCG, and CGTC. The CGCG haplotype was significantly higher in patients with SLE compared with NC (p=0.001, odds ratio=2.31). rs4945 was associated with erythrocyte sedimentation rate and rs1878327 was associated with alopecia, C-reactive protein, complement 3, anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibody, and systemic lupus erythematosus disease activity score. rs2271715 and rs3743388 were associated with renal disease, cumulated steroid dose, cyclophosphamide and mycophenolate mofetil usage and rs3743388 also was associated with anti-dsDNA antibody. Serum MFG-E8 concentration was shown significantly higher in SLE than NC (2,030.3±1,292.3 pg/mL vs 1,433.0±946.3 pg/mL, p=0.017).

Conclusions Our data suggest possibility that MFG-E8 rs2271715 and rs3743388 SNP can be involved in susceptibility of SLE. Also, these SNPs are associated with renal disease and disease activity in SLE. Furthermore, rs4945 and rs1878327 polymorphisms may be a marker of disease activity.

31 MINDFULNESS-BASED COGNITIVE THERAPY IN KOREAN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background This study aims to evaluate the effectiveness of six-session stress reduction program based on mindfulness-based cognitive therapy (MBCT) among Korean patients with systemic lupus erythematosus (SLE) who experienced chronic stress.

Methods In total, 25 patients with SLE were enrolled. The MBCT program comprised two-hour sessions and homework for six weeks. The psychological data were collected through a questionnaire that included the Korean version of the Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), Satisfaction with Life Scale (SWLS), and Perceived Stress Scale (PSS). We evaluated the effect of the MBCT on disease activity of SLE.

Results The mean scores on BDI-II, BAI, SWLS, and PSS before MBCT were 24.2±10.6, 19.1±9.7, 14.7±6.5, and 20.4±3.82, respectively. Eighteen patients with SLE completed the MBCT program. After the MBCT, their BDI-II, BAI, and PSS improved; 17.4±13.0 (p<0.01), 13.4±7.7 (p=0.04), and 17.9±4.6 (p=0.04), respectively. However, SWLS score was not changed. There was no difference in disease activity between before and after the MBCT.

Conclusions This study showed preliminary evidence on the use of the MBCT in reducing the anxiety, depression, and stress of patients with SLE but not disease activity of SLE.

32 SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF BI 705564, A COVALENT INHIBITOR OF BRUTONS TYROSINE KINASE IN PHASE 1 CLINICAL TRIALS IN HEALTHY VOLUNTEERS

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Background The small molecule BI 705564 is a highly selective, covalent and potent inhibitor (B cell CD69 activation IC50=2.2 nM) of the Brutons tyrosine kinase (BTK). BTK plays a critical role in the differentiation and function of B cells and myeloid cell lineages and may play a major role in autoimmune diseases. Blocking the BTK pathways may be a promising new treatment of autoimmune diseases like SLE.

Methods BI 705564 has been studied in 43 male healthy volunteers (HV) in a single-blinded, partially randomized, placebo-controlled trial testing single rising doses from 10 to 160 mg. In a double-blinded, randomized, placebo-controlled

study BI 705564 was administered to 50 male HV at doses from 10 to 80 mg once daily for 14 days. Blood samples were analyzed for BI 705564 plasma concentrations, BTK target occupancy (TO) and CD69 expression in B cells stimulated *ex-vivo* with anti-IgD.

Results All doses of BI 705564 were well-tolerated in both studies. There were no serious adverse events (AEs) and reported AEs were mainly of mild intensity and not dose-limiting. There was no difference in the total number of subjects with AEs (combined data from both trials) between BI 705564 [28/75 (37.3%)] and placebo [8/18 (44.4%)] and no dose-relationship of AEs. The most frequently reported AE was headache (BI 705564: 8.0% vs placebo: 5.6%, combined data). There was no difference in the occurrence of infections (BI 705564: 6.5% vs placebo: 11.1%) or gastrointestinal disorders (BI 705564: 13.3% vs. placebo 11.1%) in both studies (combined data). There were no relevant drug-related changes in vital signs, ECGs and standard safety laboratory tests. Analysis of BI 705564 plasma exposures showed a terminal half-life between 5.7 and 14.2 hour with no relevant accumulation after multiple dosing. Doses of 20 mg and above resulted in an average TO 85% which is expected to result in clinical efficacy based on preclinical studies. After a single dose administration, TO was maintained for at least 48 hour consistent with the mechanism of a covalent irreversible inhibitor. Functional effects on BTK signalling were demonstrated by dose-dependent inhibition up to 100% of CD69 expression on anti-IgD stimulated B cells.

Conclusions BI 705564 was well-tolerated in healthy subjects after single and multiple doses. The favorable clinical safety profile and the high potential based on pre-clinical studies and effects on CD69 support further investigation of BI 705564 in patients with autoimmune diseases like SLE.

risk), 2 (intermediate-risk) or 3 (high-risk). According to first follow-up, patients were further divided into increased risk, remained risk and decreased risk group. A prediction model was used to distinguish SLE-PAH from vasculitic and vasculopathic subtype, based on the time interval between the diagnosis of SLE and PAH and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). KaplanMeier survival curves and Cox proportional hazards analysis were conducted.

Results 282 patients were enrolled. The 5 year survival of patients with none, one, two, three and four low risk criteria were 42.7%, 64.8%, 86.1%, 90.2% and 91.7%, respectively (HR=0.59, 95% CI 0.44–0.78, p<0.001). The 5 year survival of patients in low-risk, intermediate-risk and high-risk group were 92.3%, 60.4% and 50.0%, respectively (Log-rank, p=0.001). Notably, in low-risk group, patients with vasculitic subtype had better survival than those with vasculopathic subtype (Log-rank, p=0.044). The 5 year survival of patients with remained, decreased and increased risk were 65.4%, 88.1% and 23.8%, respectively (log-rank, p<0.001).

Conclusions Our study, for the first time, validated the prognostic value of risk stratification strategy at baseline and follow-up visit in patients with SLE-associated PAH. Patients are recommended to have a comprehensive evaluation on PAH and SLE at baseline and every follow-up visit. The SLE disease activity and systemic manifestations predict the phenotype of SLE-associated PAH, which also effect the long-term survival and need to be involved into risk assessment of SLE-associated PAH. Improving to low-risk group can be a future treatment target for SLE-associated PAH patients in clinical practice.

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33 COMPOSITE GOALS PLUS INFLAMMATION: FURTHER RISK ASSESSMENT FOR SYSTEMIC LUPUS ERYTHEMATOSUS ASSOCIATED PULMONARY ARTERIAL HYPERTENSION IN CSTAR-PAH COHORT

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Background Chinese SLE treatment and Research Group (CSTAR) started a multi-center prospective cohort study recruiting SLE patients with pulmonary arterial hypertension (PAH) since 2006. This study aimed to investigate the validity of a multimensional risk assessment and the prognostic value of it in SLE-associated PAH.

Methods All SLE patients were fulfilled the 1997 revised ACR criteria. PAH was diagnosed based on ESC/ERS guidelines by right heart catheterization. The outcome was all-cause mortality. Two different methods of risk categorization were applied according to baseline data, including low-risk criteria number of none to four and mean score of 1 (low-

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34 EVALUATION OF ADVERSE EVENTS AND RELAPSE RISK OF SYSTEMIC LUPUS ERYTHEMATOSUS DURING TREATMENT WITH HYDROXYCHLOROQUINE

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Background The antimalarial drug hydroxychloroquine (HCQ) has been widely used in the world to control the disease activity of systemic lupus erythematosus(SLE). In Japan, it has not been approved until September 2015 due to the problem of retinopathy induced by chloroquine. For these reasons, there is insufficient evidence for its effects and adverse events.