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OP0254

A PROPENSITY SCORE-MATCHED (PSM) ANALYSIS OF ORGAN DAMAGE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) FROM THE POOLED BLISS LONG-TERM EXTENSION (LTE) TRIALS VERSUS THE TORONTO LUPUS COHORT (TLC)

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Background: A pooled analysis of the open-label BLISS LTE studies (BEL112233/BEL112234) reported low levels of organ damage accrual (measured by Systemic Lupus International Collaborating Clinics [SLICC]/American College of Rheumatology Damage Index [SDI]) in patients who received belimumab (BEL) plus standard therapy (SoC) over a 5 year period. However, the LTE studies had no SoC arm. This post-hoc study (206347) used PSM to match BLISS LTE patients to TLC patients to define a SoC treatment comparison cohort.

Objectives: To assess damage accrual in patients with SLE treated with BEL plus SoC compared with PSM patients from the TLC treated with SoC alone.

Methods: This analysis compared the mean SDI change from baseline (over 5 years), time to SDI event (on all patients with ≥ 1 year follow-up), and magnitude of year-to-year SDI change (over 5 years), from baseline to Year 5 in patients treated with BEL plus SoC (pooled United States [US] and non-US data from the BLISS LTE studies), and SoC alone. Patients in the LTE and TLC were 1:1 PSM based on 16 clinical variables with a propensity score calliper $\pm 20\%$. Regression augmented inverse propensity score weighting (IPSW) tested the robustness of the PSM results.

Results: For the 5 year analysis, 181 LTE patients were matched to 181 TLC patients (mean bias 3.8%) from a larger pool of 973 patients (BLISS LTE n=592; TLC n=381). Time-to-event PSM resulted in 323 LTE and 323 TLC patients (mean bias 3.7%) from a larger pool of 1541 patients (BLISS LTE n=949; TLC n=592). The mean SDI score change from baseline in the BEL group was 0.265 (95% confidence interval [CI]: 0.180, 0.350) compared with 0.718 (95% CI: 0.547, 0.889) in the SoC group, resulting in a BEL treatment effect of -0.453 fewer SDI units (95% CI: -0.646, -0.260; $p < 0.001$) over 5 years compared with SoC alone. The IPSW model produced similar results (-0.374, 95% CI: -0.512, -0.236; $p < 0.001$). Patients treated with BEL were 60% less likely to progress to a higher SDI score over any given year of follow-up compared with SoC patients (hazard ratio 0.397, 95% CI: 0.275, 0.572; $p < 0.001$). A patient receiving BEL has a 3.1% annual probability of organ damage progression compared with a 7.5% annual probability with SoC. Among the 646 time-to-event matched patients, there were 49 increases in SDI over the first 5 years in the BEL group and 102 in the SoC group. Of these, 4.1% (n=2/49) of the BEL group had an SDI increase ≥ 2 compared with 25.5% (n=26/102) of the SoC group. Therefore, for patients who experienced any increase, the likelihood of experiencing a ≥ 2 point SDI increase was 6-times greater in the SoC group (25.5/4.1=6.22; $p = 0.002$).

Conclusions: This PSM analysis demonstrates that BEL plus SoC reduces, and slows the rate of organ damage progression and reduces the magnitude of progression compared with SoC alone.

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OP0255

IDENTIFICATION OF CLINICAL AND SEROLOGICAL PREDICTIVE FACTORS OF RESPONSE TO RITUXIMAB TREATMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS

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Background: Response to Rituximab (RTX) varies significantly between SLE patients. Ethnicity may play a role in these differences, and a possible relationship has been suggested between the clinical response to RTX and the presence of certain auto-antibodies (ab) (anti-ENA and anti-dsDNA ab) and C3 levels at baseline.

Objectives: The aim of this study was to identify biomarkers that could predict the response to RTX treatment in SLE patients.

Methods: This was a cross-sectional study of 121 SLE patients treated with RTX in UCLH between 2000 and 2016. Demographic, clinical and serological data were analysed. Disease activity was evaluated using the BILAG index. Patients were categorised as 'Responders' if all or some of the As and Bs from the BILAG score at the time the RTX was given were lost at 6 and at 12 months, and as 'Non-Responders' if none of the As and Bs were lost. Relapse after RTX treatment was defined as development of a new BILAG Grade A or B in any system. A uni and multivariate regression analysis were performed to identify predictive factors of response to RTX utilising a combination of clinical and biological markers.

Results: At 6 and at 12 months, 85% and 70% respectively of our patients had responded clinically to the RTX treatment. 24% of patients relapsed during the year after RTX. In the univariate analysis, constitutional symptoms at diagnosis (crude OR (95% CI): 5.66 (1.53–20.88), $p = 0.009$) and the absence of musculoskeletal disease at the time of RTX (0.27, (0.09–0.81), $p = 0.019$) were related to response at 6 months. In the multivariate analysis, both remained significant, (adjusted OR (95% CI)): 5.33 (1.39–20.41), $p = 0.014$ and 0.26 (0.08–0.81), $p = 0.021$ respectively. With respect to the response at 12 months, in the univariate analysis the presence of arthritis as the main indication for RTX (3.16 (1.31–7.58), $p = 0.010$), the absence of renal disease at diagnosis (0.36 (0.15–0.86), $p = 0.022$) and of cardiorespiratory disease at the time of RTX (0.29 (0.09–0.89), $p = 0.031$), less than one anti-ENA ab (0.28 (0.12–0.66), $p = 0.003$), low levels of C3 at diagnosis (0.29 (0.09–0.89), $p = 0.031$), increased anti-dsDNA ab levels (0.38 (0.17–0.89), $p = 0.025$) and decreased C3 levels (0.27 (0.11–0.63), $p = 0.002$) before RTX were related to the response. In the multivariate analysis, only the absence of more than one anti-ENA showed significance (0.30 (0.11–0.82), $p = 0.020$). Having more than one anti-ENA was related to relapse (3.30 (1.36–8.05), $p = 0.009$), while having arthritis as the main indication for RTX therapy was associated with a lower risk of flare (0.26 (0.10–0.64), $p = 0.004$). On the multivariate analysis, having arthritis remained significant (0.29 (0.11–0.75), $p = 0.010$).

Conclusions: There is a relation between the presence of more than one anti-ENA ab and a worse response to treatment at 12 months and a higher risk of flaring. Having arthritis at the time of RTX leads to a negative response at 6 months but a lower risk of flare before 1 year.

Disclosure of Interest: None declared

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OP0256

HYDROXYCHLOROQUINE REDUCES RISK OF INCIDENT DIABETES MELLITUS IN PRIMARY SJÖGREN SYNDROME PATIENTS: A PROPENSITY SCORE MATCHED POPULATION-BASED COHORT STUDY

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Background: HCQ is an antimalarial drug that is widely prescribed for the treatment of Sjögren syndrome. Glucocorticoids may alter glucose metabolism and contribute to diabetes mellitus. Treatment for primary Sjögren syndrome (SS) sometimes requires glucocorticoids that may worsen glucose homeostasis. HCQ can reduce diabetes risk in SLE and RA.

Objectives: This study aimed to investigate the association of HCQ use and diabetes mellitus risk in primary SS patients.

Methods: This nationwide, population-based cohort study was conducted using the Taiwan National Health Insurance Research Database. In the period 2002–13, 7311 newly diagnosed primary SS patients were identified after excluding those with a previous diagnosis of RA, SLE or diabetes mellitus. The propensity score matched 4874 patients with at least 6 month hydroxychloroquine exposure after diagnosis and 2437 patients without. Incidence of diabetes mellitus was identified as a new diagnostic code using a diabetes mellitus-specific medication.

Results: Four hundred and ninety-seven newly diagnosed diabetes mellitus patients were identified among primary SS patients (4874 had taken HCQ and 2437 had never taken HCQ), with an average follow-up period of 4.9 years. Compared with patients without HCQ treatment, the hazard ratio (HR) of diabetes

mellitus in patients taking HCQ at a cumulative dose ≥ 175 g was reduced [HR 0.60 (95% CI: 0.45 to 0.80), $p < 0.001$]. Higher prednisolone-equivalent dose (≥ 88 defined daily dose) was associated with increased risk of developing diabetes mellitus [HR 1.50 (95% CI: 1.11 to 2.03), $p = 0.001$], which was reduced by concomitant HCQ use at a cumulative dose ≥ 374 g [HR 0.34 (95% CI: 0.22 to 0.56), $p = 0.001$].

Conclusions: This propensity score matched analysis of Taiwanese patients with primary SS found that use of HCQ is associated with reduced risk of incident diabetes mellitus in a dose-dependent manner. High-dose glucocorticoids increase the risk of diabetes, which can be decreased by concomitant HCQ use.

Disclosure of Interest: None declared

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OP0257

DECREASE OF AUTOPHAGY IN PERIPHERAL BLOOD MONONUCLEAR CELLS FROM SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS TREATED WITH BELIMUMAB

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Background: Autophagy is a conserved catabolic process that degrades cytoplasmic constituents and organelles in the lysosome, promoting the recycling of cellular nutrients, and is also a key mechanism for protein homeostasis and quality control¹.

T lymphocytes from patients with systemic lupus erythematosus (SLE) are resistant to induction of autophagy².

Belimumab (BLM), a human monoclonal antibody that inhibits B lymphocyte stimulator (BLyS), is the first biological drug to be approved for the treatment of SLE. BLM seems to play a role in modulating the signalling cascade involved in the regulation of autophagy, blocking the binding of soluble BLyS to its receptors (B cell activating factor receptor, BAFF-R; B cell maturation antigen, BCMA; transmembrane activator and calcium modulator and cytoplasmic ligand interactor, TACI), mainly expressed on B cells and plasmacells³.

Objectives: The aim of this study was to evaluate the autophagy process by means the expression of LC3-II and p62 markers in lysates of peripheral blood mononuclear cells (PBMCs) from SLE patients at baseline (t0) and after 2 weeks (t2weeks), 1 month (t1month), and 3 months (t3months) of treatment with BLM. We also investigated the presence of BLyS receptors on T cell subsets.

Methods: We enrolled 15 consecutive patients who started treatment with BLM (M/F, 0/15; mean age, 44.3 years, range 30–54 years; mean disease duration, 242.6 months, range 48–432 months). All patients fulfilled the American College of Rheumatology revised classification criteria⁴. PBMCs from SLE patients were lysed in lysis buffer and analysed to evaluate autophagy, monitoring LC3-II and p62 levels by Western blot. Flow cytometry was performed for surface phenotyping of freshly isolated PBMCs, using conjugated monoclonal antibodies against human CD4 and CD8; anti-human BAFF-R, BCMA, and TACI polyclonal antibodies were used to detect BLyS receptors on T cells subsets.

Results: LC3-II expression levels in PBMCs from SLE patients decreased after 3 months of BLM therapy and, in the same lapse, p62 levels increased (figure 1; $p < 0.05$ for all the experimental conditions). BAFF-R and BCMA were expressed on CD4⁺ (Mean Fluorescence Intensity -fold increase-, MFI=1.6 and 1.2, respectively; $p < 0.05$) and CD8⁺ (MFI=1.6 and 2.5; $p < 0.05$) T cells, while TACI was expressed only on CD8⁺ T cells (MFI=1.2; $p < 0.05$).

Conclusions: In the present study we demonstrated, for the first time, the expression of BAFF-R, TACI and BCMA in CD4⁺ and CD8⁺ T cells from SLE patients, and that BLM treatment was able to decrease the levels of autophagy in PBMCs. We can speculate that BLM could mediate this effect by blocking the binding of BLyS with its receptors.

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From cartilage to bone

OP0258

EFFICACY OF THE HIGHLY SELECTIVE ADAMTS-5 INHIBITOR GLPG1972 IN THE RAT MENISCECTOMY MODEL

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Background: Aggrecan cleavage is an early process in cartilage degradation observed in OA. As a result, aggrecanase inhibition is an attractive therapeutic strategy for the treatment of OA.^{1,2} A disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5) is an aggrecanase playing a key role in the catabolic events leading to OA.³ We previously described the pharmacological characterisation of GLPG1972, a potent, selective and orally bioavailable ADAMTS-5 inhibitor showing anti-catabolic activity in cartilage explants and displaying disease-modifying OA drug (DMOAD) potential in the destabilisation of the medial meniscus (DMM) model in mice.^{4,5}

Objectives: In this communication we report the activity of GLPG1972 in a second model of surgery-induced OA, the rat meniscectomy (MNX) model.⁶

Methods: OA pathology was induced by meniscectomy in the right hind leg of each rat. On day 1 post surgery, rats were randomly assigned to a treatment group (n=20 per group) according to their body weight. GLPG1972 was administered orally over 3 weeks at dose levels of 10, 25 and 50 mg/kg b.i.d. At sacrifice, the right tibias were collected and processed for histological analysis. OA development in the tibial plateau was evaluated using the OARSI score. The following structural parameters were measured by imaging histomorphometry analysis: subchondral bone plate thickness, proteoglycan content and fibrillation index. Blood samples were collected at steady state at predose, 1, 3 and 6 hour post-dose for the determination of GLPG1972 plasma concentrations.

Results: Three weeks post-surgery, a significant reduction in OARSI score compared to vehicle-treated rats was observed with GLPG1972 at 25 and 50 mg/kg b.i.d. (–24% and –23%, respectively). Treatment with GLPG1972 also resulted in a significant reduction in cartilage fibrillation as of 25 mg/kg b.i.d. and prevented proteoglycan loss and subchondral bone plate thickening at all doses. At 25 mg/kg b.i.d. GLPG1972 average plasma concentration over 24 hour was found to be in line with the value observed in other rat MNX experiments (385 ng/mL). GLPG1972 bio-distribution in the target tissue was also determined: the average condyle to plasma ratio was found to be 0.14.

Conclusions: Oral dosing with GLPG1972 in rat MNX model resulted in significant chondroprotection confirming the DMOAD potential of GLPG1972. A Phase 1 first-in-human study was successfully completed with GLPG1972 (NCT02612246), and a dose-escalation Phase 1b study in OA patients is ongoing (NCT03311009). GLPG1972 is a promising OA drug candidate and a Phase 2 program is currently under preparation.

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