AB0507

BELIMUMAB IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: OUTCOMES IN ROUTINE CLINICAL PRACTICE

C. Moriano¹, M. Garijo¹, C. Iñiguez¹, E. Díez¹, C. Díez², L. Gómez-Lechón³, J. Martín⁴, M. Corteguera⁵, O. Martínez⁶, J. Cabezas⁶, T. Pérez¹. ¹Hospital León, León; ²Hospital El Bierzo, Ponferrada; ³Hospital Salamanca, Salamanca; ⁴Hospital Río Hortega, Valladolid; ⁵Hospital Ávila, Ávila; ⁶Hospital Zamora, Zamora, Spain

Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a wide range of clinical manifestations. The persistence of activity of the disease and the prolonged use of corticosteroids are amongst the main predictors of accumulated organ damage in patients with SLE. Therefore, we need new strategies to induce long-lasting remission and minimise the adverse effects of standard medications.

Objectives: to assess the effectiveness and safety of Belimumab in actual clinical practice during the first year of treatment in patients with SLE.

Methods: retrospective observational study of patients treated with Belimumab. This study involves 6 hospitals in Castilla y León (Spain). It collects clinical and analytical data before the start of Belimumab, and 6 and 12 months after the initiation of the therapy. The data collected include the daily dose of prednisone received at different time points and the activity of the disease was classified as mild, moderate and severe based on SELENA-SLEDAI index. A reduction from baseline of 3 points on the SELENA-SLEDAI indicates meaningful symptomatic improvement.

Results: Among the twenty-five patients were included, with a mean age of 43.7 ± 12.2 years, 72% were female and 96% caucasian. The average time from diagnosis of SLE to Belimumab infusion was 9.5 ± 7.1 years; 32% were diagnosed with SLE < 5 years ago. Up to 56% of the patients had moderate disease activity and only 8% patients had very high activity of the disease. All but one of the patients had previously received an immunosuppressant (azathioprine in 50% of the cases) and 16% of the sample had not responded to rituximab. The most frequent reasons for initiating Belimumab were an ineffective previous treatment regimen (60%), the intend to decrease steroid use (56%), and worsening patient condition (52%); whereas the most frequent manifestation of SLE in these patients were arthritis (44%), followed by mucocutaneous (20%) and immunologic findings (20%). As for immunologic markers of activity, DNA was elevated by 40% and 68% of the patients showed hypocomplementemia, that dropped to 24% in both cases at 12 months. The mean score of the SELENA-SLEDAI index decreased from 9.5 to 6 in the first 6 months and to 5.2 in the 12 months of follow-up. A reduction in the initial mean steroid dose was also observed from 20 mg/day to 8.9 mg/day and 6.4 mg/day at 6 and 12 months respectively. Hence, the dose of steroid was reduced by 68% during the first year (p=0.06). This reduction was clinically significant, but it did not reach statistical significance in our study. Two patients (8%) had discontinued Belimumab within the first 6 months of therapy (1 pregnancy and 1 worsening proteinuria); 34.7% had discontinued it within the first 12 months, mostly due to ineffectiveness (62.5%). Two patients with severe renal involvement (>1 gr proteinuria/24 hour) were treated with Belimumab, allowing to reduce the steroids to a low dosis (<7.5 mg/day) at 12 months.

Conclusions: Belimumab appears to be effective, reducing disease activity as measured by the SELENA-SLEDAI Index and, also, the mean dose of steroids needed, mainly after 12 months of treatment. No significant adverse effects were reported as previous studies have shown.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.7530

AB0508

FIXED, LOW-DOSE HYDROXYCHLOROQUINE VERSUS WEIGHT-ADJUSTED DOSE IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITH LOW ACTIVITY

J.L. Callejas-Rubio¹, D. Sanchez-Cano¹, R. Ríos-Fernández¹, M. Moreno-Higueras², G. Fatoul del Pino¹, S. Velasco-Fuentes¹, M. Trigo-Rodríguez¹, N. Faro-Minguéz¹. ¹Unidad de Enfermedades Autoinmunes Sistémicas; ²Servicio de Medicina Interna, Hospital Campus de la Salud, Granada, Spain

Background: Optimal hydroxychloroquine (HCQ) dose to reduce ocular toxicity risk is 5 mg/kg or actual weight daily, according to new recommendations. In systemic lupus erythematosus patients (SLE) with low or no disease activity, fixed low-dose HCQ might be equally effective in relapse prevention weight-adjusted doses, thus resulting in lower cumulative dose.

Objectives: Our aim was to compare a fixed dose of HCQ 200 mg daily with a weight-adjusted dose (5 mg/kg of actual weight daily) in SLE patients with low activity.

Methods: SLE activity was assessed using the SLE Disease Activity Index (SLEDAI-2K), the Safety of Oestrogen in Lupus Erythematosus National Assessment (SELENA)-SLEDAI and the Physician Global Assessment (PGA, 0–3 scale) in each visit. Low-activity SLE (LLDAS) was defined according to Franklyn et al: 1) a SLEDAI-2K score ≤ 4, 2) no new SLE-related activity events compared with the previous visit, 3) a PGA score ≤ 1, 4) prednisone dose ≤ 7.5 mg daily and 5) stable

doses of maintenance immunosuppressant therapy. LLDAS was evaluated at baseline and months 3 and 6. In order to adjust doses to weight, and given the impossibility of fractionating HCQ tablets, the adjusted dose was calculated for every week. For example, for 62 kg patient, the calculated dose would be 5 mgx52 kg=260 mg daily, which would mean 1820 mg weekly. Therefore, the patient would receive 400 mg daily for 2 days and 200 mg daily for 5 days every week. A relapse was defined as an increase of SLEDAI scores ≥ 3, according to current recommendations

Results: A total of 50 LLDAS patients were compared, 25 with a fixed dose and 25 with a weight-adjusted dose. No significant differences regarding body weight between groups were observed: 52 kg (41–58.5 kg) vs. 51 kg (44–55 kg). Baseline activity scale scores were not significantly different. No patient relapsed on follow-up in either of both groups. Finally, the mean HCQ cumulative dose at 6 months was reduced by approximately 9.6 grams.

Conclusions: In LLDAS patients, a fixed HCQ dose of 200 mg daily may be as effective as the weight-adjusted dose in preventing disease relapses, thus resulting in a decrease in the HCQ cumulative dose and, therefore, a reduction of the risk of ocular toxicity.

REFERENCE:

- [1] Franklyn K, Lau CS, Navarra SV, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). *Ann Rheum Dis*. 2016;75:1615–21.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.7414

AB0509

KZR-616, A SELECTIVE INHIBITOR OF THE IMMUNOPROTEASOME, SHOWS A PROMISING SAFETY AND TARGET INHIBITION PROFILE IN A PHASE I, DOUBLE-BLIND, SINGLE (SAD) AND MULTIPLE ASCENDING DOSE (MAD) STUDY IN HEALTHY VOLUNTEERS

J. Lickliter¹, D. Bomba², J. Anderl², A. Fan², C.J. Kirk², J. Wang². ¹Nucleus Network, Melbourne, Victoria, Australia; ²Kezar Life Sciences, South San Francisco, California, USA

Background: Proteasome inhibition is a standard of care for plasma cell malignancies. Bortezomib targets the constitutive proteasome and immunoproteasome, and is effective in the treatment of Systemic Lupus Erythematosus (SLE) and lupus nephritis (LN), but is associated with hematologic (e.g. thrombocytopenia) and constitutional (e.g. peripheral neuropathy) adverse events (AEs).

Objectives: We report the safety, pharmacokinetics (PK), pharmacodynamics (PD) and immunomodulatory effects of KZR-616, a first-in-class selective inhibitor of the immunoproteasome, in healthy volunteers (HV) following single and repeat subcutaneous (SC) administration.

Methods: Cohorts (6 drug:2 placebo) received single or 4 weekly SC doses. Safety assessments, PK and PD were measured to Day 7 (SAD) or Day 28 (MAD). SAD cohorts included 7.5, 15, 30 and 60 mg (SC). MAD cohorts included 30, 45, 60 mg, and 2 intrasubject escalation cohorts with 1 dose at 30 mg and 3 doses at 45 mg. PK was measured by LC/MS². PD was measured using enzymatic and active site binding assays. Inflammatory cytokine release was measured following *ex vivo* stimulation of whole blood in HV receiving placebo or 45 mg KZR-616.

Results: 32 HV (24:8) were enrolled in 4 SAD cohorts. The most common AEs were injection site reactions (ISRs), which were generally mild and transient. No clinically-significant (CS) laboratory or ECG abnormalities and no dose limiting toxicities were observed in the SAD subjects. Following SC administration, drug exposure increased dose proportionally and was characterised by rapid absorption (T_{max} 15–30 min) and clearance (T_{1/2} ~2 hours). Inhibition of the immunoproteasome exceeded 80% at ≥ 30 mg with significant recovery noted over 7 days. Constitutive proteasome inhibition was <37% in all cohorts.

40 HV (30:10) were enrolled in 5 SC MAD cohorts. In the initial cohort of 60 mg, a systemic drug reaction (chills, elevated heart rate, nausea) occurred ~8 hours after the first dose in 4 subjects. Dosing for this cohort was stopped. Subsequent cohorts (initiated at 30 mg) received prophylactic treatment with antihistamines ± prednisone 1 hour prior to the first and second dose. No similar AEs occurred with repeat dosing of 45 mg. No CS laboratory or ECG abnormalities were seen in the remaining MAD cohorts. ISRs did not appear to increase in severity or frequency with repeat dosing. There were no AEs of peripheral neuropathy, and 45 mg was well tolerated across 3 cohorts.

Consistent PK was noted following repeat administration and no drug accumulation was observed. At 45 mg, inhibition of 2 key subunits of the immunoproteasome, LMP7 and LMP2, was ~95% and ~70%, respectively. Reduced *ex vivo* stimulated production of multiple cytokines (IL-23, IL-6, TNF-α, IL-17) was noted in subjects receiving repeat administration of 45 mg KZR-616.