A NOVEL TLR7/8 ANTAGONIST BLOCKS PRO-INFLAMMATORY FUNCTION OF IMMUNE COMPLEXES FROM LUPUS PATIENTS AND ABROGATES LUPUS-LIKE DISEASE IN MICE

**Keywords:** Inmate immunity, Disease-modifying drug (DMARDs), Systemic lupus erythematosus

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**Background:** Toll-like receptors (TLR) 7 and 8 are innate sensors of single stranded RNA (ssRNA). Genetic and in vivo evidence suggests that aberrant recognition of RNA-containing autoantigens by TLR7/8 drives autoimmune diseases (Junt and Barchet, 2015). More validation for a pathogenic effect of TLR7 in chronic inflammation comes from recent data showing that a TLR7 gain-of-function mutation is sufficient to drive lupus-like disease (Brown et al., 2022).

**Objectives:** Here we report on the preclinical characterization of MHV370, a highly selective, orally active TLR7/8 inhibitor for treatment of chronic inflammatory diseases.

**Methods:** We used a suite of in vitro profiling assays to investigate the effect of MHV370 on TLR responses. This included the stimulation of PBMCs by immune complexes from systemic lupus erythematosus patient sera. Furthermore we characterized MHV370 in different mouse models of acute and chronic TLR7-driven inflammation.

**Results:** In vitro, MHV370 interfered with TLR7/8-dependent production of cytokines in humans and mice, most notably of interferon alpha, a clinically validated driver of autoimmune diseases. MHV370 abrogates B cell, monococyte, and neutrophil responses downstream of TLR7/8. In vivo, prophylactic or therapeutic administration of MHV370 suppressed TLR7-dependent cytokines and interferon production across mouse models of lupus. MHV370 prevented halled disease progression and glomerulonephritis. Unlike hydroxychloroquine, MHV370 interfered with cytokine production triggered by immune complexes between systemic lupus erythematosus patient sera and necrotic cell extract, suggesting differentiation from clinical standard of care.

**Conclusion:** The pharmacological data presented here support further development of MHV370 towards clinical proof of concept trials in man.

**REFERENCES:**

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SUBTHERAPEUTIC HYDROXYCHLOROQUINE CONCENTRATION IS ASSOCIATED WITH INCREASED DISEASE ACTIVITY AND GREATER ORGAN DAMAGE DURING 5-YEAR FOLLOW-UP IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

**Keywords:** Systemic lupus erythematosus

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**Background:** Hydroxychloroquine (HCQ) is a cornerstone drug in patients with systemic lupus erythematosus (SLE), as it decreases the risk of flares and comorbidities and improves survival. This study investigated the effects of the serum HCQ concentration on clinical manifestations, disease activity, and organ damage in a longitudinal cohort of SLE patients.

**Methods:** The 338 SLE patients from the Korean Lupus Network registry were assessed with respect to their demographic data, clinical and laboratory findings, PGA score, and adjusted mean SLEDAI-2000 (AMS) and SLICC damage index scores annually for 5 consecutive years. Patients were divided into two groups according to their serum HCQ concentration at baseline: patients with a subtherapeutic level (< 500 ng/mL) and those with a therapeutic level (try were assessed with respect to their demograhic the clinical outcomes was evaluated in a longitudinal analysis using a generalized estimating equation (GEE) and a logistic regression analysis.

**Results:** Of the 338 patients, 287 (84.9%) were in the subtherapeutic group at baseline. This group had a higher incidence of newly developed lupus nephritis (P = 0.036) and had been prescribed higher mean and cumulative doses of prednisone (P = 0.003 and P = 0.013) than the therapeutic group. In multivariable analyses based on GEE, an association of the subtherapeutic group with both a higher PGA score (β coefficient = 0.328, 95% confidence interval CI): 0.215–0.441, P < 0.001) and a higher SLICC damage index score (β coefficient = 0.366, 95% CI: 0.061–0.671, P = 0.019) was determined across all 5 years. In the multivariate logistic regression analysis, subtherapeutic HCQ was significantly associated with the AMS (odds ratio [OR] = 1.142, 95% CI 1.022–1.276, P = 0.199), mean PGA (OR = 3.897, 95% CI 1.767–7.735, P < 0.001), and an annual increase in the SLICC damage index score (OR = 1.529, 95% CI 1.005–2.325, P = 0.047).

**Conclusion:** A subtherapeutic HCQ concentration may affect the development of new-onset LN, and had the significant association with higher disease activity and cumulative organ damage in these SLE patients over time.

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**Disclosure of Interests:** None Declared.

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SPANISH NATIONAL REGISTRY OF BELIMUMAB IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

**Keywords:** Registries, Systemic lupus erythematosus

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