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THU0219 FIRST-INHUMAN STUDY OF SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF IRAK1/4 INHIBITOR R835 IN HEALTHY SUBJECTS

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Background: Toll-Like Receptors (TLR) and Interleukin-1 Receptors (IL-1R) play a critical role in the innate immune response as microbial and tissue damage sensors, providing a bridge between the innate and adaptive immunity. Interleukin receptor associated kinases (IRAK) 1 and 4 are serine/threonine kinases that are essential for signaling downstream of most TLRs and IL-1Rs and the resulting production of pro-inflammatory cytokines. Suppression of TLR and IL-1R signaling through inhibition of IRAK1/4 kinases is a promising therapeutic approach for the treatment of inflammatory and autoimmune diseases. We have identified a potent and selective IRAK1/4 inhibitor (R835) that showed dose-dependent inhibition of lipopolysaccharide (LPS, a TLR4 agonist), and IL-1 β induced serum cytokines in mice. R835 prevented disease onset and progression in multiple rodent models of inflammatory diseases, including arthritis and lupus models.

Objectives: The aim of this FIH study was to characterize the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of R835 after single or multiple dose oral administrations.

Methods: This study was a randomized, placebo-controlled, double-blind Phase 1 study in healthy subjects in three parts: single ascending doses (20 mg-1920 mg, Part A) with food effect in a separate cohort (480 mg), multiple ascending doses (120 mg and 960 mg, BID, Part B) with a caffeine interaction (960 mg cohort), and an intravenous LPS challenge test at 240 mg oral dose of R835 (Part C).

Results: Single doses of up to 480 mg R835 in organic solution, single doses of up to 1920 mg R835 as capsule, multiple doses of 120 mg R835 Q12H (organic solution), and 960 mg R835 Q12H (capsule) were safe and well tolerated. All R835 related adverse events (AEs) were mild in intensity and reversible, and mostly associated with the higher doses of R835 in the organic solution. The most common AEs were headache and gastrointestinal disturbance. The PK of R835 was linear and dose proportional in exposure over the dose range studied. A nominal level of accumulation in plasma achieved rapidly upon repeated BID administrations with steady-state essentially attained in 2 days. A high-fat meal with the capsule formulation resulted in slow rate of absorption but had no effect on the extent of absorption. There was no effect of R835 on metabolism of caffeine (P450 CYP1A2 prototype substrate). In the LPS challenge test, R835 profoundly inhibited the acute release of cytokines, including TNF- α , IL-6, IL-8, MIP1 α and MIP1 β , but had no impact on CRP release.

Conclusion: R835 was well tolerated after single or multiple dose administrations. The most common AEs were headache and gastrointestinal disturbance. For both of the formulations tested, the PK of R835 was linear and exposure was dose proportional with rapid steady-state attainment following BID administration. There was no drug-drug interaction by use of caffeine as the prototype substrate. R835 inhibited the LPS induced release of cytokines in the serum, including TNF- α , IL-6, IL-8, MIP1 α and MIP1 β , mirroring preclinical data in mice. The desirable PK and safety profile combined with proof of mechanism, as demonstrated by inhibition of cytokine release, support progression of R835 into Phase II clinical development as an agent for the treatment of inflammatory and autoimmune diseases.

Disclosure of Interests: Lucy Yan Shareholder of: Amgen, Rigel, Employee of: Amgen, Rigel, Sandra Tong Shareholder of: Rigel, Employee of: Rigel, Anthony Absalom: None declared, Izaak den Daas: None declared, Gary Park Shareholder of: Rigel Pharmaceuticals, Employee of: Rigel Pharmaceuticals, Vanessa Taylor Shareholder of: Rigel Pharmaceuticals, Employee of: Rigel Pharmaceuticals, Donna Chow Shareholder of: Rigel, Employee of: Rigel, Meng Lee Shareholder of: Rigel, Employee of: Rigel, Hanzhe Zheng Shareholder of: Rigel, Employee of: Rigel, Andrew Chow Shareholder of: Rigel, Employee of: Rigel

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SLE, Sjögren's and APS - etiology, pathogenesis and animal models

THU0220 AUTOPHAGY IN SJÖGREN'S SYNDROME SALIVARY GLAND EPITHELIAL CELLS (SGECs) IS ASSOCIATED WITH THE SEVERITY OF INFLAMMATION AND EPITHELIAL CELLS ACTIVATION.

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Background: Sjögren's Syndrome (SS) is characterized by chronic inflammation supported by intrinsic activation of salivary gland epithelial cells (SGECs). Eventually, apoptosis of SGECs ensues, which leads to salivary gland dysfunction and exposition of autoantigens. Autophagy is a stress coping mechanisms of cells implicated in both survival and exposition of autoantigens, and is thereby plausibly implicated in the pathogenesis of SS. At present, the exact relationship between apoptosis and autophagy in SS SGECs is unclear, as is the link between these mechanisms and SGECs activation.

Objectives: To explore autophagy in SGECs from patients with SS and to evaluate its relationship with apoptosis and SGECs activation.

Methods: Consecutive patients with suspected SS referring to our "Sjogren Clinic" were enrolled, and minor salivary gland (MSG) biopsies were collected for: (1) SGECs culture, (2) PCR analysis, (3) IFI analysis. In SGECs cultures, the expression of autophagy (LC3II), apoptosis (annexin V/PI) and adhesion molecules (ICAM) was investigated by flow cytometry (results expressed as mean % $\pm$ SD). The expression of the autophagy gene MAP1LC3II was evaluated by PCR (expressed as 2^{-deltaCT} normalized to GAPDH) on both MSG sections and MSG acinar and ductal epithelium samples obtained by laser capture microdissection. Tissue expression of LC3II was evaluated by IFI on SS MSG.

Results: Primary SGECs cultures were established from 14 MSG obtained for diagnostic purposes (SS n=8, Sicca n=6). These cells exhibited an inverse correlation between apoptosis and autophagy (p=0.007, r=-0.784), with lower levels of apoptosis (19.7 $\pm$ 6.5 vs 24.5 $\pm$ 8.5, p=ns) and higher levels of autophagy (59.7 $\pm$ 13.1 vs 54.19 $\pm$ 19.4, p=ns) in SS compared to Sicca. In SS, MAP1LC3 was positively correlated with Focus Score (p=0.021 r=0.478); however, PCR studies did not reveal significant differences in MAP1LC3 expression between SS (n=26) and Sicca (n=15) (0.024 $\pm$ 0.010 vs 0.022 $\pm$ 0.008, p=ns). Ductal SGECs (n=4) isolated by laser microdissection of MSG revealed a higher expression of MAP1LC3 (0.005 $\pm$ 0.0005 vs 0.003 $\pm$ 0.0008; p=0.057) compared to normal acinar epithelium (n=5); a major expression of LC3II in ducts was confirmed by IFI (Image).

In SS, a higher expression of ICAM compared to sicca was observed (11.1 $\pm$ 3.8 vs 6.9 $\pm$ 6.9, p=0.006) and autophagy and apoptosis showed a trend of positive and negative correlation with this molecule, respectively (p=0.683 r=0.118 and p=0.106 r=-0.446).

Figure. LC3-II staining in SS MSG [LC3-II+ (green) and Hoechst stain (blue); 60x magnification].

Conclusion: In SS, autophagy is upregulated in SGECs and inversely correlated with apoptosis, thus supporting a role of this process in cells' death prevention during inflammatory process. Indeed, the degree of msg inflammation is correlated more with the activation of autophagy than apoptosis. Interesting, in SS, SGECs autophagy is mainly observed at ductal level and is correlated with