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FRI0016

R835, A NOVEL IRAK1/4 DUAL INHIBITOR IN CLINICAL DEVELOPMENT, BLOCKS TOLL-LIKE RECEPTOR 4 (TLR4) SIGNALING IN HUMAN AND MOUSE

C. Lamagna¹, C. Gundel¹, M. Chan¹, C. Young¹, S. Braselmann¹, R. Frances¹, S. Yi¹, Y. Chen¹, G. Park¹, L. Chou¹, E. Masuda¹, Y. Taylor¹. ¹Rigel Pharmaceuticals, South San Francisco, United States of America

Background: Toll-Like Receptors (TLR) and Interleukin-1 Receptors (IL-1R) play a critical role in the innate immune response as microbial sensors, providing a bridge between the innate and adaptive immunity (1). 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 (2). 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.

Objectives: The aim of the study was to characterize the effects of R835, a novel small molecule inhibitor of IRAK1/4, on TLR4 signaling.

Methods: R835 was identified in cell-based assays measuring cytokine production induced by LPS (TLR4 ligand). Inhibition of IRAK1 and IRAK4 kinases by R835 was confirmed in biochemical assays and cell lysates. The ability of R835 to inhibit TLR4 signaling was further evaluated in human and mouse whole blood assays. R835 was tested in a mouse model of LPS-induced cytokine release. Mice were pre-treated orally with vehicle or R835 prior to challenge with LPS and serum cytokine levels were monitored over a 24-hour period.

Results: We have identified R835, a selective small molecule inhibitor of IRAK1 and IRAK4. R835 blocked LPS/TLR4 signaling and the resulting production of proinflammatory cytokines in both human and mouse cells and whole blood. R835 suppressed serum cytokine elevation in mice challenged with LPS.

Conclusion: Our study demonstrates that R835, through inhibition of IRAK1/4 kinase activity, blocks LPS-induced cytokine production in vitro and in vivo. In a recent phase 1 study, R835 substantially reduced the increase of serum cytokines after an intravenous LPS challenge in healthy volunteers. Importantly, this shows that the pharmacological inhibition of IRAK1/4 pathway by R835 in humans mirrors the results obtained in mice. To our knowledge, R835 is the first dual IRAK1/4 inhibitor to enter clinical development and demonstrate inhibition of TLR4-induced cytokines in both mice and humans. R835 is a promising clinical candidate that will allow the exploration of IRAK1/4 inhibition in the treatment of cytokine-driven rheumatic and autoimmune diseases.

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Employee of: Rigel Pharmaceuticals, Chi Young Shareholder of: Rigel Pharmaceuticals, Employee of: Rigel Pharmaceuticals, Sylvia Braselmann Shareholder of: Shareholder of Rigel Pharmaceuticals, Employee of: Employee of Rigel Pharmaceuticals, Roy Frances Shareholder of: Rigel Pharmaceuticals, Employee of: Rigel Pharmaceuticals, Sothy Yi Shareholder of: Rigel Pharmaceuticals, Employee of: Rigel Pharmaceuticals, Yan Chen Shareholder of: Rigel Pharmaceuticals, Employee of: Rigel Pharmaceuticals, Gary Park Shareholder of: Rigel Pharmaceuticals, Employee of: Rigel Pharmaceuticals, Lu Chou Shareholder of: Rigel Pharmaceuticals, Employee of: Rigel Pharmaceuticals, Esteban Masuda Shareholder of: Rigel Pharmaceuticals, Employee of: Rigel Pharmaceuticals, Vanessa Taylor Shareholder of: Rigel Pharmaceuticals, Employee of: Rigel Pharmaceuticals

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FRI0017

ACTIVATION OF TOLL-LIKE RECEPTORS IN PERIPHERAL BLOOD MONONUCLEAR CELLS OF TAKAYASU ARTERITIS PATIENTS

Y. Tian¹, J. Li², X. Tian², X. Zeng². ¹Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Rheumatology, Beijing, China; ²Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Department of Rheumatology, Beijing, China

Background: The activation of self-specific T cells is essential in pathogenesis of Takayasu arteritis (TAK). Dendritic cell (DC) plays an indispensable role as the only antigen presenting cell for initial T cell, and Toll-like receptors (TLRs) are common source of activation signals for DCs. Then we speculate that there are activation of TLRs in TAK patients.

Objectives: To investigate the activation of TLRs in TAK patients.

Methods: Twenty-seven TAK patients were enrolled during April to October in 2019, with diagnosis met the 1990 criteria of American College of Rheumatology. Patient were divided into groups by the disease activity and medication history. Disease activity was assessed by the 1994 NIH criteria. Quantitative Real-time Polymerase Chain Reaction (RT-qPCR) was used to analyze the mRNA relative abundance of 28 target genes in peripheral blood mononuclear cells (PBMCs). Differences between groups and correlation between any two genes were analyzed.

Results: The demographic data and clinical features of TAK patients were shown in Table 1. (1) Compared with health control (HC) group, mRNA abundance of *TLR2*, *TLR4*, *P50*, *P65*, *IkBa*, *CTLA4*, *CD3*, and *BCL6* in untreated TAK group was upregulated (<0.05), whereas mRNA abundance of *CD40* was downregulated (<0.05). (2) Compared with HC group, mRNA abundance of *TLR2*, *TLR4*, *IkBa*, *PD-1* and *BCL6* in treated TAK group was upregulated (<0.05), whereas mRNA abundance of *LAG3*, *CD40* and *TCR* was downregulated (<0.05). (3) Compared with untreated TAK group, mRNA abundance of *P50*, *P65*, *CD28*, *CTLA4*, *TLR2*, *TLR4*, *IkBa*, *PD-1* and *RORC* was upregulated in treated TAK group (<0.05). (4) Compared with non-active treated TAK group, mRNA abundance of *p50*, *CD28*, *TCR*, *GATA3*, *RORC* and *FOXP3* was upregulated in nonactive treated TAK group (<0.05). *BCL6* showed correlation with the TLRs-NFκB pathway. (Figure 1–2, Table 2)

Table 1. Demographic data and clinical features of patients with TAK

	Age (year)	Gender (male/ female)	Disease duration* (months)	ESR (mm/h)	hs-CRP* (mg/L)	Interleukin 6 (pg/mL)	TNFα(pg/ mL)	Prednisone	
								used/ non-used	Dosage (mg/d)
Treated (n=20)	39.37±9.27	1/19	43 (12, 103)	14.60±8.94	1 (0.55, 5.625)	2.1 (2, 3.95)	7.56±4.39	18/2	10 (10, 32.5)
Active (n=11)	39.30±7.889	1/10	118 (16, 166.5)	16.82±10.81	5.63 (1.49, 8.33)	3.15 (2.025, 5.775)	8.42±5.57	10/1	10 (10, 15)
Nonactive (n=9)	39.44±10.59	0/9	40 (12, 44)	11.89±4.61	0.84 (0.31, 1)	2 (2, 2.4)	6.60±2.11	8/1	8.75 (6.875, 16.25)
P value	0.89	—	0.16	0.34	0.02	0.08	0.65	—	0.37
Untreated (n=7)									
Active (n=4)									
1	31	M	—	91	140.72	—	—	—	0
2	25	F	—	19	11.28	6.3	5.2	—	0
3	23	M	—	71	77.36	6.3	6.2	—	0
4	29	F	—	127	113.62	22.2	8.4	—	0
Nonactive (n=3)									
5	34	F	—	7	0.34	2	4.3	—	0
6	27	F	—	14	0.16	25.7	4	—	0
7	38	F	—	5	0.32	3	4	—	0

* median (min, max)