Anti-NASH Effects of Solithromycin in NASH-HCC Mouse Model

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Prabhavathi Fernandes[1], Taishi Hashiguchi[2], Masato Fujii[2], Hiroyuki Yoneyama[2]
[1]Cempra Inc., NC, USA. [2]Stelic Institute & Co. Inc., Tokyo, Japan

BACKGROUND: Non-alcoholic steatohepatitis (NASH) is a progressive form of non-alcoholic fatty liver disease (NAFLD) where accumulation of excessive fat (steatosis) coexists with liver cell injury, inflammation and fibrosis, which eventually leads to cirrhosis and hepatocellular carcinoma. To date, no single therapy has been approved for treating NAFLD/NASH. Solithromycin (SOLI) is a next-generation oral and intravenous fluoroketolide in Phase 3 clinical development for the treatment of community-acquired bacterial pneumonia. In the present study, we evaluated SOLI in a diabetic mouse model of NASH-HCC (STAM™ model) to investigate its potential effects on the liver disease. SOLI is well tolerated in patients with mild to severe hepatic impairment and no significant differences in safety, compared to healthy controls, are noted. Additionally, no dosage adjustment is needed when administering SOLI to patients with mild, moderate, or severe hepatic impairment. SOLI has been demonstrated to have potent anti-inflammatory properties in addition to its antibacterial properties. In the present study, we evaluated SOLI in a diabetic mouse model of NASH-HCC (STAM™ model) to investigate its potential effects on this liver disease.

METHODS: NASH was induced in male mice by a single injection of streptozotocin 2 days after birth, followed by a high fat diet from 4 weeks of age (STAM™ model; Fujii M et al., *Med Mol Morphol,* 2013; 46: 141-152). At 5 weeks of age, 16 mice were divided into two groups; one group was administered vehicle, the other group was administered 50 mg/kg SOLI orally once a day for 4 weeks. Animals were sacrificed at 9 weeks of age, and biochemical, histological and gene expression analyses were performed.

RESULTS: The SOLI treated group had marked improvements in hepatocellular ballooning ($P<0.0001$) and inflammatory cell infiltration ($P<0.01$). Administration of SOLI had no effect on body weight or body weight changes, but significantly decreased mean liver weight and the mean liver-to-body weight ratio compared to the vehicle group. Furthermore, treatment with SOLI improved glucose metabolism as evidenced by reduction of whole blood glucose levels. These changes were accompanied with a significant improvement in the histological score of NASH (NAFLD Activity Score [NAS]). There was no difference in triglycerides between the SOLI treated and vehicle treated mice. MCP-1 and MMP9 mRNA expression levels were significantly decreased in the liver.

CONCLUSION: SOLI has demonstrated potential anti-NASH and anti-hyperglycemic effects in the present study. Because NAS is a clinical endpoint used to assess the treatment of NASH, these observed changes in the treatment group suggest potential for SOLI in the treatment of NASH.

	Liver Weight (mg)	Liver-to-body Weight Ratio (%)	Whole Blood Glucose Levels (mg/dL)	NAFLD Activity Score
Vehicle	1391 ± 124	7.0 ± 0.4	628 ± 85	5.4 ± 0.5
Solithromycin	1242 ± 141*	6.0 ± 0.7*	380 ± 170**	3.0 ± 0.9***

Values are means ±SD. *P<0.05, **P<0.01, ***P<0.0001