Mechanism of Action of the Anti-NASH effects of Solithromycin in a Predictive NASH HCC Mouse Model

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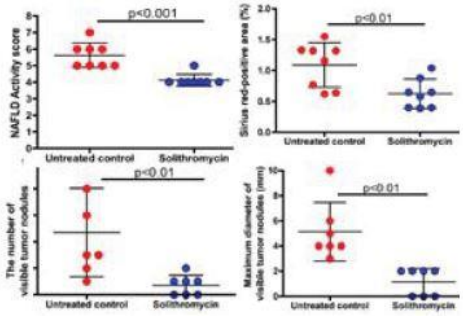
Background/Introduction: Solithromycin (SOLI) significantly reduces NAFLD Activity Scores (NAS) by decreasing hepatic ballooning degeneration and blood glucose in a NASH mouse model. This report describes the reduction of fibrosis and HCC and identifies the mechanism for glucose reduction.

Methods: NASH was induced in mice by injecting streptozotocin, followed by a high fat diet for 4 weeks. NASH mice were treated between 4-8 weeks, 8-12 weeks or 4-20 weeks with 100 mg/kg QD. and with lower doses. Biochemical, histological and gene expression analyses were done at end of treatment.

Results: A significant response to SOLI was observed for multiple parameters influencing NASH, metabolic syndrome, fibrosis and HCC. Hyperglycemia, hepatocyte ballooning degeneration, fibrosis and neutrophil infiltration were all significantly reduced. Serum insulin levels were undetectable, while hepatic expression of glucose-6-phosphatase (G6pc) and fructose 1,6 biphosphatase (FBPase) were significantly suppressed. Liver-to-body ratio percent and serum triglyceride were significantly reduced. MCP-1gene expression was significantly decreased. Expression of genes associated with fibrosis regulation was unaffected. Mice treated from 8-12 weeks also showed significant declines in NAS scores and significantly decreased fibrosis (Figure). Mice treated with 100 mg SOLI QD from weeks 4-20 showed a significant decrease in tumor nodules (Figure).



Conclusion: SOLI significantly decreased blood glucose, inflammation, NAS score, fibrosis and HCC. Reduction in G6pc and FBPase gene expression points to suppression of hepatic gluconeogenesis as the mechanism of hyperglycemia improvement. A proof-of-concept human trial is planned.

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