



CF102 an A₃ Adenosine Receptor Agonist Acts as a Potent Inhibitor of Hepatitis C Virus Replication and has Excellent Pharmacokinetic Properties

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Background: The Gi protein associated A₃ adenosine receptor (A₃AR) is highly expressed in autoimmune inflammatory diseases and cancer. A₃AR over expression is found in the pathological tissue and is reflected in the peripheral blood mononuclear cells (PBMCs) of the patients. Targeting A₃AR with highly specific and selective nucleoside agonists induces marked anti-inflammatory and anti-cancer effects.

Objectives: To look at A₃AR expression levels in PBMCs of HCV infected patients and to examine the effect of CF102, an A₃AR nucleoside agonist on HCV replication. The safety and pharmacokinetic profile of CF102 was tested in a Phase I study in healthy volunteers.

Methods: A₃AR protein expression levels in patients' PBMCs was measured by Western Blot analysis. The anti-viral effect of CF102 was tested in a cell-based selectable subgenomic HCV RNA Huh-7 replicon system. Viral replication was monitored in intact cells by the SEAP enzymatic assay. We further analyzed the anti viral effect of CF102 using Huh-7 cell infected with HCV in which the viral copy number was evaluated by RT-PCR analysis.

Results: A₃AR was highly expressed in PBMCs derived from HCV infected patients in comparison to those of healthy subjects. A₃AR over-expression was found to be directly correlated with high expression levels of NF-κB, known to act as a transcription factor of A₃AR. CF102 inhibited HCV replication both in the Replicon system with an IC₅₀ of 0.1 pM and in the HCV infected Huh-7 cells, with an IC₅₀ of 10pM . CF102, orally administered to healthy subjects was found to be safe and well tolerated. At doses of 1-40 mg the pharmacokinetic profile was linear, reaching a blood level of 134.6 ng/mL at the highest dose group. The half life time of CF102 was found to be 12 hours.

Conclusions: Taken together, these data demonstrate that CF102 is an attractive candidate for further development as a potential treatment for HCV infection.