Treatment with the Anti-miRNA122 Oligonucleotide RG-101 Results in a Decrease in IP-10 but Does Not Affect the Levels of Other Cytokines in Patients with Chronic Hepatitis C.

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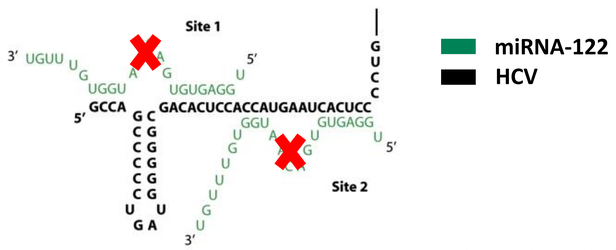
INTRODUCTION

MicroRNA-122 is an important host factor that binds to the hepatitis C virus (HCV) enabling the replication of HCV. RG-101, an oligonucleotide targeting miR-122, may be a new therapeutic option for patients with chronic hepatitis C (CHC). Exogenous oligonucleotides however, may potentially trigger innate immune sensors in the host, by acting as pathogen-associated molecular patterns (PAMPs). In preclinical studies, RG-101 showed no induction of inflammatory genes in rats dosed with RG-101.[1] However, it is important to know the nature of any immunological changes observed in patients dosed with RG-101.



Adapted from Machlin et al, PNAS 2011

AIM

In this study we analyzed whether an immunological response is measurable in the plasma of patients with CHC who were dosed with RG-101.

MATERIALS & METHODS

Patients with chronic hepatitis C who participated in a phase 1 study received a single subcutaneous injection with RG-101.

14 patients received 2 mg/kg, 14 patients 4 mg/kg, and 2 patients in each group received placebo. Plasma samples were collected at baseline, Day 3, 8, 29 and 57. For comparison, plasma samples from 6 healthy controls were included in the analyses.

Plasma levels of IL-12, MCP-1 (CCL2), MIP-1a (CCL3), MIP-1b (CCL4), ICAM-1 (CD54), IP-10 (CXCL10), GM-CSF, IFN-alpha, IFN-gamma, IL-1alpha, IL-1 beta, IL-10, IL-13, IL-17A, IL-4, IL-6, IL-8, e-selectin (sCD62E), p-selectin (sCD62P) and TNF-alpha were measured using a Luminex 20-plex immunoassay (Affymetrix eBioscience, San Diego, USA). HCV RNA levels were measured using Roche COBAS AmpliPrep/COBAS Taqman HCV v2.0 assay, with a reported LLOQ of 15 IU/mL.

RESULTS

1. IP-10 levels decline upon dosing with RG-101

At baseline, patients with CHC had significantly higher IP-10 levels compared to healthy controls (median 58,08 and 19,33 pg/mL respectively, p<0.0001). After dosing with RG-101, at Day 8, IP-10 levels had declined significantly as compared to placebo (which had 1.12 fold reduction) in both the 2 mg/kg (2.13 fold reduction, p=0.0046) and 4 mg/kg group (2.56 fold reduction, p=0.004).

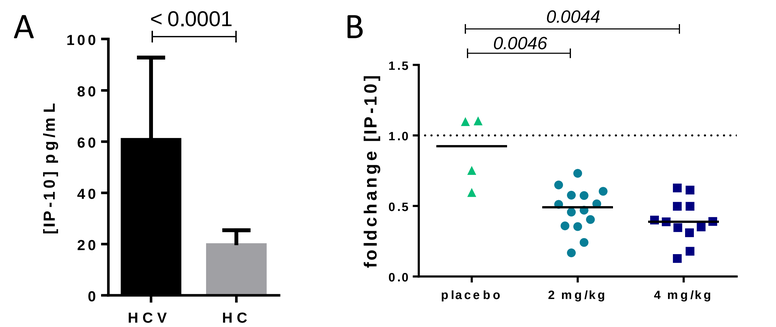


Figure 1. (A) Baseline IP-10 concentration (Mann-Whitney U test) (B) fold change in IP-10 levels at Day 8 in placebo, 2 mg/kg and 4 mg/kg RG-101 dosed CHC patients.

2. IP-10 decrease is independent of HCV RNA decline

The decrease in IP-10 was independent of HCV RNA decline (Pearson r=0.07, p=0.15). Furthermore, the decrease in IP-10 was similar between patients with and without HCV RNA below the limit of quantification at 57 (Week 8) (2.38 and 2.17 fold reduction respectively, p=0.64).

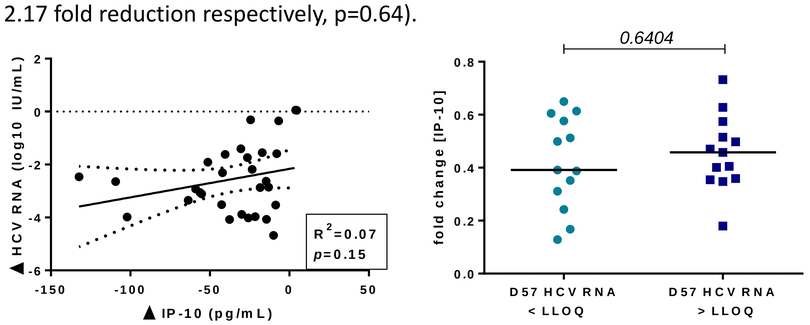


Figure 2. (A) Change in HCV RNA and IP-10 levels at Day 8 after dosing. (B) fold change in IP-10 plasma levels at week 8 comparing day 57 responders and non-responders (Mann-Whitney U test).

3. No other cytokine fluctuations were measurable in the plasma after dosing with RG-101

For other cytokines and chemokines at baseline no differences between healthy controls and patients with CHC were observed, and no differences were observed in CHC patients upon dosing with RG-101. After dosing with RG-101, no differences were observed in CHC patients dosed with 2 or 4 mg/kg or placebo.

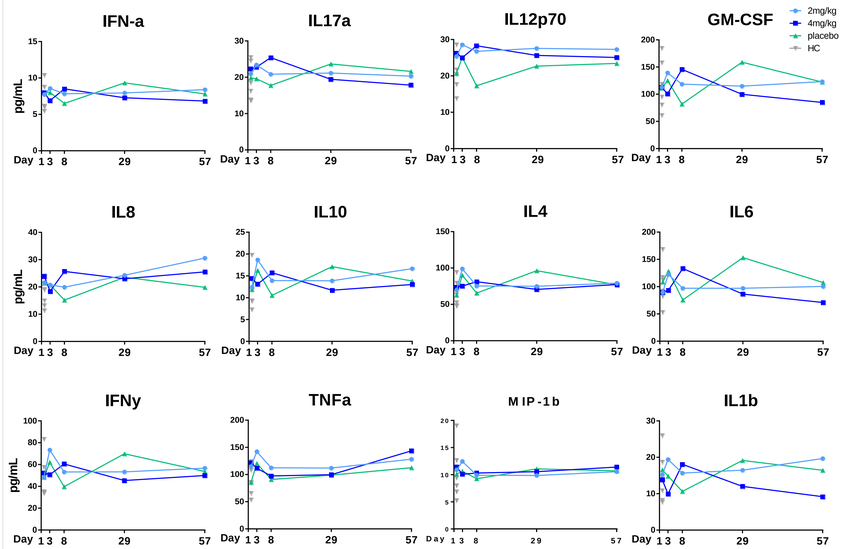


Figure 3. Longitudinal measurements of different cytokines in plasma of CHC patiënts during follow-up after a single dose of RG-101. Plasma levels of IFN-alpha, IL-17a, IL12p70, GM-CSF, IL-8, IL-10, IL-4, IL-6, IFN-gamma, TNF-alpha, MIP-1b (CCL4) and IL-1b were similar between patients dosed with RG-101 and placebo.

CONCLUSION

1. RG-101 does not trigger any undesirable systemic immune activation in CHC patients.
2. CHC patients have significantly higher plasma IP-10 levels at baseline compared to healthy controls.
3. In CHC patients dosed with RG-101, a significant decline was observed in IP-10 concentrations compared to baseline. This was independent of HCV RNA decline.

References:
1. S. Neben et al. J Hep 2015; 62: P0907

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