A single dose with anti-miR122 oligonucleotide RG-101 results in a less activated phenotype of NK cells in patients with chronic hepatitis C

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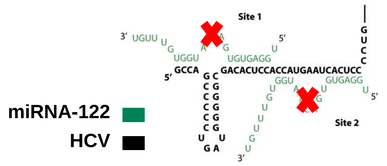
BACKGROUND

In patients with chronic hepatitis C (CHC), natural killer (NK) cells express an altered phenotype[1]. This phenotype has been shown to normalize after successful DAA treatment[2].

Here we analysed the changes in the phenotype of NK cells in CHC patients who received a single dose of the anti-miRNA122 oligonucleotide RG-101.



Adapted from Machlin et al, PNAS 2011

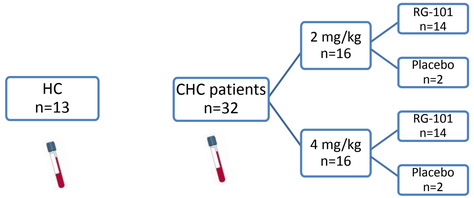
OBJECTIVES

To analyse the changes in the phenotype of NK cells in CHC patients who received a single dose of RG-101.

MATERIALS & METHODS

Patients with chronic hepatitis C who participated in a phase 1 study received a single subcutaneous injection with anti-miR-122; RG-101.

14 patients received 2 mg/kg, 14 patients 4 mg/kg, and 2 patients in each group received placebo. PBMC s were collected at baseline, Week 2 and Week 8. Phenotypic analyses on NK cells were performed by flowcytometry. Thirteen healthy controls (HC) were added for comparison.



RESULTS

1. HCV RNA declines, NK cells increase

After dosing with RG-101, the HCV RNA load declined in all patients. Furthermore 12/19 patients had a HCV RNA < BLOQ at Day 57. The total proportion of NK cells increased after dosing. While the proportion of CD56^{dim} NK cells increased during follow-up, the proportion of CD56^{bright} cells was significantly lower at Week 8 after injection as compared to baseline.

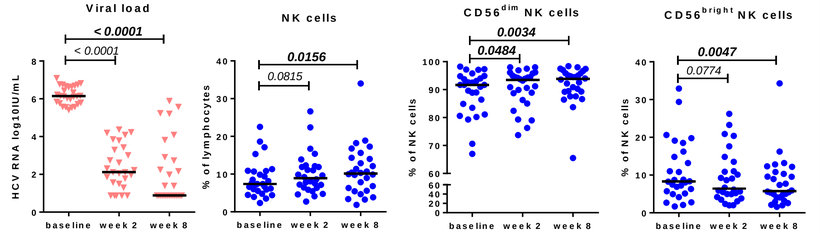


Figure 1. Baseline, week 2 and week 8 HCV RNA load, proportion of NK cells and NK cell subsets in patients who received RG-101. Wilcoxon signed rank test.

2. Decrease in TRAIL expression

At Week 8 the expression of TRAIL, an important ligand for the induction of apoptosis, on CD56^{bright} NK cells had decreased significantly as compared to baseline (median 13.3 to 6.6 % of CD56^{bright} NK cells, p<0.0001). No differences were observed in baseline TRAIL expression between patients with HCV RNA <BLOQ and >BLOQ at Week8.

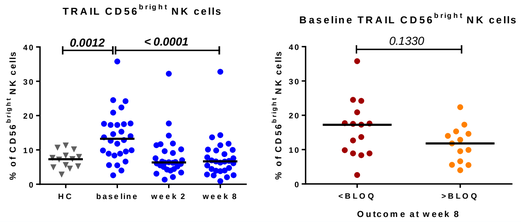


Figure 2. (A) TRAIL expression on CD56^{bright} NK cells in healthy controls (HC) and CHC patients treated with RG-101. (B) baseline TRAIL expression in patients with and without HCV RNA below the limit of quantification (BLOQ) at Week 8. Mann Whitney / Wilcoxon signed rank test.

3. Decrease in activation of NK cells

The expression of the Fcγ-receptor CD16 on NK cells decreased after dosing with RG-101. The expression of CD27, as well as the expression of natural cytotoxicity receptors NKp30 and NKp46 also decreased on NK cells after dosing with RG-101.

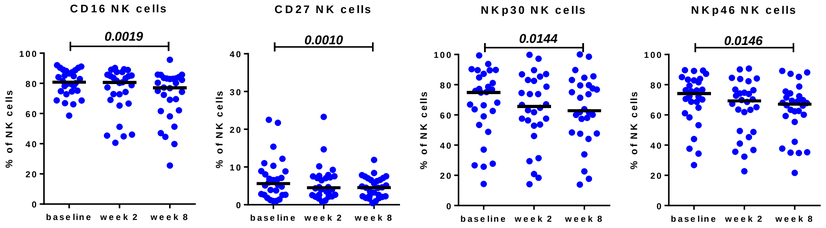


Figure 3. Expression of CD16, CD27, NKp30 and NKp46 on NK cells. Wilcoxon signed rank test.

CONCLUSIONS

- In patients with chronic hepatitis C, a single dose of RG-101 leads to a reduction in HCV RNA in all patients.
- Upon dosing with RG-101, the NK cell phenotype shift towards a less activated phenotype, similar to what has been shown in patients with viral load decline upon DAA treatment.

REFERENCES

1 Rehermann, *Nature Medicine* 2013
2 Spaan et al., *Journal of Infectious Diseases* 2015

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