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No change in HCV-specific T cell functionality after successful DAA treatment in chronic hepatitis C patients.

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Background and aims: In patients with chronic hepatitis C (CHC) infection, plasma IP-10 levels are increased, reflecting a state of prolonged immune activation. As a result of constant immune activation, virus-specific T cells are exhausted and functionally inactive. Here we analysed the changes in IP-10 levels as well as HCV-specific T cell function in CHC patients who were successfully treated with DAA's.

Methods: In this multicenter, investigator-initiated study, 29 patients with HCV genotype 1 (n=11), 3 (n=17) or 4 (n=1) infection were treated with sofosbuvir and daclatasvir ± ribavirin for 12 or 24 weeks (HCV genotype 3 with cirrhosis for 24 weeks). 18 patients had previously participated in a phase 1 study where they received a single subcutaneous injection with anti-miR-122 (RG-101). Plasma and peripheral blood mononuclear cells were collected at various time points during and after treatment. IP-10 levels were measured by ELISA, and *ex vivo,* HCV-specific T cell responses were quantified across the whole HCV genome using genotype specific peptides in IFN-γ ELISpot assays.

Results: All patients had an SVR12 after treatment. At baseline, IP-10 levels in CHC patients were significantly elevated as compared to healthy controls (median 134.0 and 39.4 pg/mL respectively, p<0.0001). During DAA treatment, IP-10 levels rapidly declined (-42.22 pg/mL at week 1) but were still elevated at FU week 24 after end of treatment as compared to healthy controls (median 53.82 and 39.4 pg/mL respectively, p=0.02). At baseline, functional T cell IFN-γ responses were low in CHC patients, the sum of T cell responses was median 103 SFU/ 10^6 PBMC. By week 12 of follow-up, functional T cell IFN-γ responses did not change significantly as compared to BL when assessed by ELISpot assay (88 SFU / 10^6 PBMC, p=0.38). The median change between BL and FU week 12 was -75 SFU / 10^6 PBMC (range -562 to +190 SFU).

Conclusions: After successful DAA treatment, broad immune activation reduces in CHC patients. The magnitude and functionality of *ex vivo* HCV-specific T cell responses does not increase following

successful DAA treatment. Our data suggests that there is no restoration of HCV adaptive immunity after sustained virological response in CHC patients.