Immunomodulatory Effects of Pegylated Interferon-α and Ribavirin on Th1 and Th2 Cytokine Responses to Chronically Infected Hepatitis C Patients

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Introduction & Objectives

Hepatitis C virus (HCV) is a life-threatening pathogen, because of its high prevalence and serious complications of persistent infection. Viral clearance is characterized by a vigorous T cell response. Standard treatment involves a combination of pegylated interferon-α (PEG-IFN) and ribavirin. Mechanisms underlying the synergistic effects of these drugs are still not well understood; in addition to direct antiviral mechanisms, immunomodulatory effects of both drugs seem important, with a possible shift from Th2- to Th1-cytokine profiles in successfully treated patients. We aimed to explore the relationship between Th1-Th2 cytokine profiles and response to anti-HCV treatment. The objective was to ascertain whether cytokine profiles can either dampen or aid the viral response to drug therapy.

Methods

Of 36 patients who received drug treatment, 27 responded successfully while 9 were non-responders. Peripheral blood mononuclear cells obtained before and after treatment for 1 year were stimulated with a mitogen to elicit cytokine production. Levels of IL-2, IL-4, IL-6, IL-10, IL-17A, IL-7F, IFN-γ and TNF-α were estimated using a Multiplex ELISA consisting of dyed microspheres conjugated with anti-cytokine antibodies.

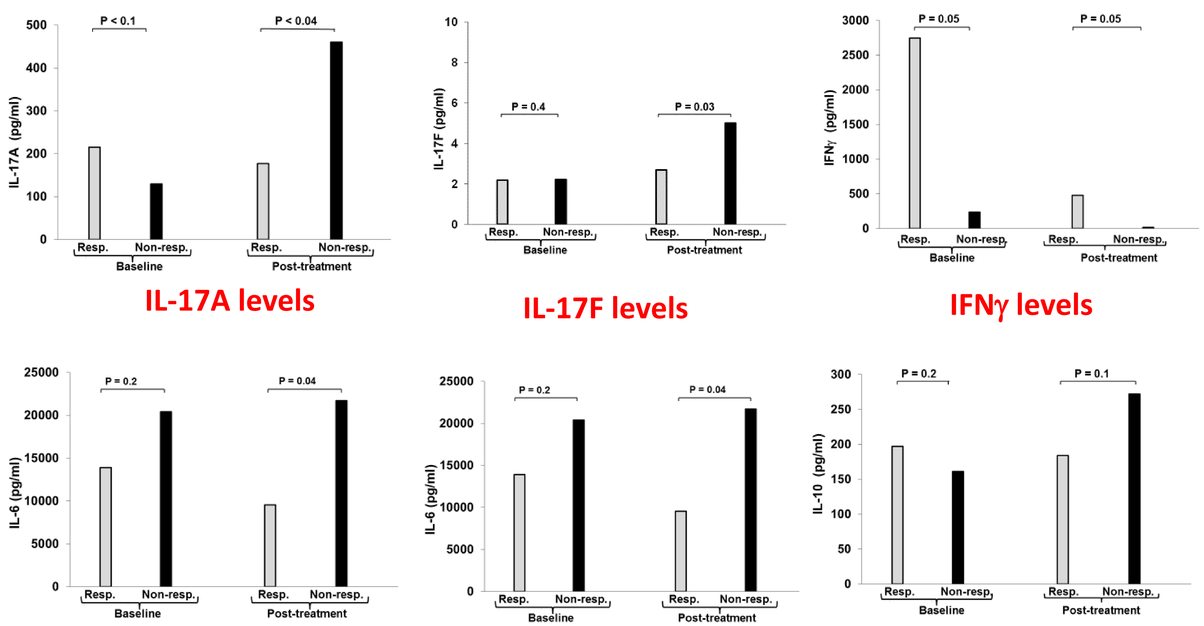
Results

Th1 Cytokines: Higher levels of IL-17A and IL-17F were produced by non-responders at the end of the treatment, i.e. at one year. IFN-γ levels were significantly higher in responders, both at baseline and at the end of treatment. TNF-α and IL-2 levels were not significantly different in responders vs. non-responders.

Th2 Cytokines: IL-4 and IL-6 levels were in patients who did not respond to the drug treatment, when measured at the end of treatment. Levels of IL-10 are not significantly different, though there was a trend towards higher IL-10 production.

Cytokine Ratios: Relative levels of cytokines may be more important than absolute levels per se. Baseline IFN/IL-4 and IFN/IL-10 ratios are higher in responders and IFN/IL-4, IFN/IL-6 and IFN/IL-10 ratios are higher at the end of treatment; this suggests a stronger Th1-biased pattern in patients who respond favorably to the treatment.

Results



Mean cytokines levels produced by PBMC from patients who responded to drug treatment (Resp) and those who did not respond (Non-resp) measured before treatment (Baseline) and at the end of treatment for 1 year (Post-treatment).

Conclusion

Increased levels of the Th1-type pro-inflammatory cytokine IFN-γ and decreased levels of the Th2-type anti-inflammatory cytokine IL-4 in responders to drug treatment supports the concept that patients who respond to drug treatment have a pro-inflammatory cytokine bias. Interestingly, high levels of IL-17A and IL-17F were associated with poor response to treatment; this supports a recent study showing a positive correlation between HCV RNA titer and IL-17 and with progressive exacerbation of HCV-induced liver damage.

IFN/IL-4 and IFN/IL-10 ratios are higher in responders as compared to non-responders suggesting that responders to drug treatment had a stronger bias towards Th1-type reactivity. This study suggests that IFN-γ and the IFN/IL-4 ratio may be considered a predictor of viral responsiveness to drug treatment.

We started with the working hypothesis that the host cytokine profile can either aid or dampen the viral response to drug therapy. Our conclusion is that host immune responses, as reflected by cytokine production patterns, appear to be associated with drug effectiveness; better response to drug treatment is associated with a stronger pro-inflammatory cytokine profile.

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