Silibinin May Abolish the Enhanced Expression of Fibrosis-Related Molecules Cause by Hepatitis C Virus E2 Protein

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Background: Chronic infection of hepatitis C virus (HCV) may lead to hepatic fibrosis and the precise mechanisms remain unclear. Our previous study indicated that E2 protein may involve in the hepatic fibrogenesis via an up-regulation of fibrosis-related proteins.

Methods: To further confirm this finding, E2 gene silencing and a treatment with silibinin was conducted on E2-expressing cells and RT-PCR analysis was performed.

Results: E2-enhanced expression of fibrosis-related molecules, including alpha-SMA, collagen alpha(I), TGF-beta1, connective tissue growth factor (CTGF), IL-6 and IL-10, MMP-2, were all abolished by a treatment with siRNA specific for E2. Furthermore, a treatment with silibinin, a potent antioxidant, was conducted to gain similar results.

Conclusion: These results further prove that E2 protein may involve in the process of hepatic fibrogenesis and E2-related fibrosis may be, at least in part, through an oxidative damage-related pathway.

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TGF-Beta1 Down-Regulates NKG2D Killer Activator Receptor Expression on Peripheral Blood Cytotoxic Cells in Patients with Chronic Hepatitis

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Introduction: Impaired natural killer (NK) cell activity contributes to viral persistence in HCV infection. Recent studies demonstrated that in tumors regulatory T cells (Treg) - via secreting TGF-beta1 - down-regulate NKG2D killer activator receptor and are responsible for poor NK cytotoxicity. Since in chronic hepatitis C plasma TGF-beta1 level is increased, we analyzed the expression of NKG2D on NK and T cells and its correlation with the percentage of Treg cells and TGF-beta1 levels.

Methods: The peripheral CD4+CD25high+ Treg cells, NKG2D+ NK and T cells were determined by FACS, plasma TGF-beta1 levels by ELISA. Forty three patients with active chronic hepatitis C, 10 sustained virological responders (SVR) and 15 healthy controls were enrolled.

Results: In patients with chronic hepatitis C the NKG2D expression was down-regulated both on NK (7.9 vs. 20.9%) and T cells (18 vs. 26.3%) compared to controls. Impaired expression of NKG2D was associated with increased proportion of CD4+CD25high+ Treg cells (4.6 vs. 3.1%) and increased TGF-beta1 levels (15 vs. 9 pg/ml) compared to controls. TGF-beta1 inversely correlated with NKG2D expression on NK cells. In SVR group, the percentage of Treg cells (1.7 ± 0.2%), TGF-beta1 levels (11.6 pg/ml) and NKG2D expression (NK:17%, T:20.9%) were comparable to controls.

Discussion/Conclusion: Our data suggest that TGF-beta1 - secreted by regulatory T cells - may be responsible for impaired NK cell function via down-regulating NKG2D. Thus, TGF-beta1 antagonism or soluble NKG2D ligands may provide the basis of a novel immunotherapy to improve the function of NK and T cells in chronic hepatitis C.

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Seven-Year Experiences on Antiviral Treatment for Chronic Viral B and C Hepatitis in Hungary - A Nation-Wide Study

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Objective: A nation-wide retrospective analysis has been performed in order to assess the efficacy of antiviral therapy for patients with chronic hepatitis B and C representing the entire population that needed treatment in Hungary, during a seven-year period. In addition, results of a prospective study including patients with chronic hepatitis C are also presented.

Patients and Methods: Of 220 patients with hepatitis B, 112 were treated with standard interferon-alpha (IFN), 23 with pegylated interferon-alpha-2a (PEG-IFN) and 85 with lamivudine (LAM), and the ratio of HBsAg seroconversion and/or undetectable HBV-DNA has been assessed. Of 2442 patients with hepatitis C, 333 were treated with IFN monotherapy, 1122 with IFN + ribavirin (RBV) and 987 with PEG-IFN + RBV for 6–12 months. In the prospective study, 69 patients with chronic hepatitis C were enrolled and treated with PEG-IFN alfa-2a + RBV. The rate of sustained virological response (SV), the predictors of outcome and the adverse effects of treatment were evaluated.

Results: For HBV patients IFN, PEG-IFN and LAM provided 31, 30, and 33% SVR rate, respectively. In hepatitis C,
a continuous improvement was noted in sustained virological response, from 13% with IFN monotherapy to 31% with PEG-IFN + RBV, while even a 48% sustained virological response has been achieved in the prospective trial. The predictors of outcome were the 4-week 'rapid' and 12-week 'early' virological responses, female gender, age, BMI and adherence. The most frequent complications of the treatment were cytopenia, haemolysis and depression, occurring in 9% of patients.

**Conclusion:** Unlike in HBV infection, in HCV hepatitis the efficacy of antiviral treatment has gradually improved in our everyday clinical practice. To manage the growing populations of hard-to-treat patients with chronic viral hepatitis, there is a need for more effective treatment modalities, including optimised, individualised dosing and novel antiviral agents.

**References:**

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**PEG-IFN Plus Ribavirin Treatment Down-Regulates Serum Fibrosis Markers Independently of Virological Response in Chronic Hepatitis C**

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**Aims:** Since in the outcome of chronic hepatitis C virus (HCV) infection the progression of hepatic fibrosis is essential, and interferon (IFN) treatment is supposed to inhibit fibrogenesis, we wanted to change in three non-invasive fibrosis markers in chronic HCV hepatitis.

**Methods:** Plasma levels of TGF-beta1 and hyaluronic acid (HA) were determined by ELISA, procollagen-III-peptide (P-III-P) levels by RIA in 49 patients with chronic hepatitis C before the antiviral treatment and 1, 3, 6 and 12 months thereafter. Twenty two patients became responders (R), 27 patients were non-responders (NR). Thirty healthy controls were also studied. Correlation between TGF-beta1, HA, P-III-P levels and the histological activity and the fibrosis score in liver biopsy was evaluated.

**Results:** Pretreatment plasma TGF-beta1, HA and P-III-P levels were significantly (p < 0.01) increased in both responder and non-responder patients compared to controls. HA levels correlated with fibrosis score, TGF-beta1 with histological activity index. PEG-IFN + ribavirin treatment decreased both TGF-beta1 and HA levels, not only in responders but also in non-responders. The reduction of fibrosis marker levels was more considerable after 6 months of antiviral therapy, and remained sustained even 6 months after the treatment.

**Conclusion:** PEG-IFN plus Ribavirin treatment decreased TGF-beta1 and hyaluronic acid levels independently of virological response. These data suggest that antiviral treatment may have antifibrotic effect even in virological non-responders.