IP-10 PROTEIN AT CHRONIC HEPATITIS C AND ITS ROLE IN FORECASTING TREATMENT OUTCOMES

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ПРОТЕИН IP-10 ПРИ ХРОНИЧЕСКОМ ВИРУСНОМ ГЕПАТИТЕ С И ЕГО РОЛЬ В ПРОГНОЗИРОВАНИИ РЕЗУЛЬТАТОВ ТЕРАПИИ

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Clinical values were identified for serum levels of γ interferon-induced protein (IP-10) to be employed in forecasting SVR to AVT for CHC, which was carried out involving 107 patients (50 females and 57 males); mean age – 43.0±11 yrs. 75 of the patients were diagnosed with genotype 1 HCV (G1), while 32 patients were identified as having non-1 genotype HCV (G2 or G3). The IP-10 levels in blood serum were detected with the ELISA method. Patients with CHC had significantly higher blood IP-10 levels compared to healthy people, and that depended on the aminotransferases’ activity as well as on the stage of hepatic fibrosis. A standard AVT with pegIFN-α medications and ribavirin given to 52 patients with G1 (SVR 54.9 %) and 27 – with G2 or G3 (SVR 75 %), showed that the patients who had reached SVR had their initial levels of IP-10 below that of non-responders. The prognostic level of IP-10 was detected, above which the likelihood of ending up at SVR in case of AVT with pegIFN-α and ribavirin was questionable: ≤ 403 pg/ml for G1 and ≤ 433 pg/ml for G2 or G3. In 18 patients who were given triple AVT – pegIFN-α + ribavirin + viral proteases inhibitors (SVR – 77.7 %) the initial levels of IP-10 at various outcomes of AVT were the same. Therefore, in case of CHC, the levels of blood IP-10 are elevated and depend on cytolysis activity and the degree of hepatic fibrosis. The levels of IP-10 protein in case of CHC may be used as a predictor regarding the standard AVT outcomes.

Key words: chronic hepatitis C, chemokines, antiviral therapy, prognosis

Определялось клиническое значение сывороточных уровней интерферон-г ′ индуцированного протеина (IP-10) в прогнозировании устойчивого вирусологического ответа (SVR) на противовирусную терапию (ПВТ) хронического вирусного гепатита С (ХВГС) у 107 больных (50 женщин и 57 мужчин), средний возраст – 43,0±1,1 лет. У 75 был диагностирован генотип 1 HCV (G1), у 32 пациентов – не-1 генотип HCV (G2 или G3). Содержание IP-10 в сыворотке крови определяли методом ELISA. Содержание IP-10 в крови больных ХВГС значительно превышало показатели здоровых и зависело от активности аминотрансфераз и стадии фиброза печени. Стандартная ПВТ с препаратами ПегИФН-α и рибавирином у 52 пациентов с G1 (SVR 54,9 %) и 27 – с G2 или G3 (SVR 75 %) показала, что у больных, достигших SVR, исходный уровень IP-10 был ниже, чем у нон-респондеров. Определен прогностический уровень IP-10, выше которого вероятность достижения SVR при ПВТ ПегИФН-α и рибавирином сомнительна: ≤ 403 пг/мл при G1 и ≤ 433 пг/мл при G2 или G3. У 18 больных, получивших тройную ПВТ: ПегИФН-α/рибавирин + ингибиторы вирусных протеаз (УВО – 77,7 %), исходное содержание IP-10 при разных результатах противовирусной терапии не различалось. Таким образом, при ХВГС уровень в крови IP-10 повышен и зависит от активности цитолиза и выраженности стадии печёночного фиброза. Содержание белка IP-10 при ХВГС может быть использовано в качестве предиктора исходов стандартной ПВТ.

Ключевые слова: хронический вирусный гепатит С, хемокины, противовирусная терапия, прогноз

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the race, hepatic steatosis, insulin resistance (if present), IL-28B genotype, the blood levels of vitamin D, and (IP-10) γ-interferon-inducible protein, CXCL10 [4, 15].

IP-10 protein (CXCL10/IP-10) is a chemokine playing an important role in eliminating HCV infection. The protein is produced by various cells – hepatocytes, T-lymphocytes, natural killers (NK), and monocytes [9, 26]. IP-10 is produced by hepatocytes as a response to hepatitis C infection [22], while the circulating levels of protein correlate with the expression of IP-10 matrix RNA (mRNA) in the hepatic tissue [3]. Involved in immune inflammation, IP-10 as a chemokine attracts to the hepatic tissue not so many of neutrophils but, more actively, T-lymphocytes, NKS and monocytes [1, 16].

In cases of acute hepatitis C, patients with higher plasma levels of IP-10 were not capable of spontaneous HCV clearance and were viewed as candidates for early antiviral therapy, while the low levels of protein were associated with potential recovery [8]. In patients suffering from CHC who were co-infected with HIV, the initial level of IP-10>400 pg/ml was a highly specific and sensitive predictor for SVR (sustained virologic response) in case of standard AVT [19]. High blood levels of IP-10 in case of CHC are also known to be in correlation with the viremia level and the severity of hepatic fibrosis [20]. The issue related to the inefficiency of IP-10 hyperproduction for elimination of HCV still remains unclear. There reports available telling about possible limitation of T-cells' functional activity under continuous impact that chronic HCV infection has on immunity due to CXCL10/IP-10 circulating in the patients’ blood in its alternated type (antagonistic for the receptor) [5, 18].

Clarifying the role played by increased production of IP-10 in the clinical presentation of CHC may prove useful in terms of developing forecast for the disease course. Detecting of IP-10 levels in patients with CHC may serve an important predictor for selecting not only an efficient yet also a cost-efficient AVT mode.

Aim of study: to identify the clinical values for IP-10 serum levels in terms of forecasting sustained virologic response to antiviral therapy offered to patients with chronic hepatitis C.

Material and Methods. 107 patients with CHC were studied (50 females and 57 males; mean age – 43.0±1.1). Most of them (75) were infected with genotype (G) 1 HCV (G1): 73 patients – 1b, 2 patients – 1a+1b. Non-1 genotype HCV (G 2 or 3) was diagnosed in 32 patients: 25 had Genotype 3 of the virus, while another 7 revealed genotype type HCV (G 2 or 3). The level of viral load was measured in IU/ml, the mean value for viremia was Ig 6.6±0.1. The study included no patients displaying signs of being infected with hepatitis B virus – HBsAg, HBV-DNA. The average ALT activity was 82.98±8.11 U/l, AspAT – 64.72±5.54 U/l. All the patients underwent liver elastometry (SuperSonic Imagine Aixplorer, France); advanced stages of fibrosis (F 3 and F 4, METAVIR) were detected in 32 patients (29.9 %), while complete hepatic cirrhosis (HC) was diagnosed in 16 patients. All the patients with HC had their liver function compensated; patients with sub- and decompensated pathology were not included in the study.

A standard AVT with PegIFN and ribavirin medications (PegIFN/RBV) was given to 52 patients with G1 HCV, and to 27 patients with non-1 genotype. The standard therapy course was 48 weeks for genotype 1 HCV, and 24 weeks – for G 2 or 3. The medication doses were administered subject to the current standards [7]. 18 patients with Genotype 1 HCV were given the triple therapy mode – pegIFN-α + ribavirin + viral protease inhibitors (while 12 patients were given telaprevir, 3 – boceprevir, 3 – sitemprevir). In the group of cases with hepatitis C that were given three antiviral drugs, 7 of the patients had previous history of failed treatment with the standard combination of antiviral medications.

The control group included 18 basically healthy persons with no markers of viral hepatitis.

The IP-10 levels in the blood serum were identified with the ELISA method employing commercial test systems (Bioscience, Austria).

The statistical processing of the results was done using the software Microsoft Office Excel 2007 with Attestat 10.5.1, IBM SPSS Statistics 21 incorporated. The values for the blood levels of IP-10 showed abnormal distribution, for which reason they were presented as a median (Me) with an interquartile range (25th and 75th percentiles); the two groups were compared employing Mann-Whitney U-test. The differences were accepted as statistically significant at p<0.05. The correlation analysis was performed with Spearman rank correlation evaluation – rs. The ROC-analysis (Receiver Operator Characteristic) with ROC curve built was used to calculate the optimal value of the cutoff threshold.

Results and Discussion. The blood levels of IP-10 in patients with CHC was significantly above the similar indices obtained from the control group: 291 (229–435) pg/ml vs. 170.5 (145; 184.5) pg/ml; p<0.0001 (Fig. 1). These outcomes were predictable and matched the data obtained earlier [5, 12, 13, 20, 21]. The HCV genotype had no impact on the IP-10 levels in blood; the protein values in the groups of patients with genotype 1 and non-1 HCV were no different either. Hyperproduction of IP-10 at CHC is initiated via the stable influence that HCV has on the patient’s immunity. The link between the level of viremia and IP-10 in the blood of patients with CHC was reported by A. I. Romero et al. [20]. Our study revealed a positive weak correlation between the viral load level and the blood IP-10 (rS= 0.24; p= 0.032). An investigation of the dependence between the serum levels of IP-10 and the biochemical features of hepatitis activity – serum aminotransferases, revealed a weak yet reliable direct correlation between the aminotransferases’ activity indicators: respectively, with the ALT activity – rs = 0.23 (p = 0.035) and the AspAT activity – rs = 0.29 (p = 0.007). A number of earlier research showed a connection between the histological activity index (HAI) in the liver tissues and the IP-10 levels at CHC [19, 24], while the hepatocytes expressing CXCL10/IP-10 in hepatic lobules were prevailing in the inflammation areas [26]. This serves a logic proof to the dependence that we revealed between protein levels and cytolytic activity.

Fig. 1. Blood levels of IP-10 in patients with chronic viral hepatitis C.
Top high serum levels of IP-10 were detected in patients with advanced stages of fibrosis (F 3–4) – 435 (283–656) pg/ml (Fig. 2). The serum levels of IP-10 are known to have shown correlation not with the histological activity index (HAI) alone but also with the fibrosis stage in patients with Genotype 1 HCV [19, 24]. Besides, we found a correlation between the blood levels of IP-10 and the fibrosis stage on METAVIR – $r_{s} = 0.373$ (p = 0.0009). The negative impact that IP-10 has on the treatment given to patients with hepatitis C co-infected with HIV and who further reached SVR, was much lower than in those who later proved to be non-responders [25]. Similar outcomes were yielded after giving PegIFN/RBV treatment to patients with CHC with no HIV [12, 14, 20].

### References


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