

Predictive Value of some Cytokines in the Course and Treatment of Chronic Hepatitis C

Gocha Barbakadze, George Kamkamidze,**
Wolfgang Stremmel****

* Thoracoabdominal Clinic, Tbilisi State Medical Academy, Tbilisi, Georgia,
** Department of Clinical Immunology, REA Rehabilitation Center, Tbilisi, Georgia,
*** Clinic of Internal Medicine IV, University of Heidelberg, Germany

Abstract

It is widely assumed that cellular immune response and cytokine (especially proinflammatory cytokines) production play an important role in the course and treatment effectiveness of chronic hepatitis C infection. 92 patients with chronic HCV infection have been investigated. Our investigations showed that after 6 weeks from the initiation of the treatment by pegylated interferon- α in the combination with ribavirin, concentration of serum cytokines IL-1 β , IL-6 and IL-18 have significantly changed and at the end of the treatment concentration of all cytokines have decreased and this change was statistically significant for all cytokines.

Keywords: *chronic hepatitis C, cytokines, predictive factors*

Introduction

Hepatitis C virus (HCV) is a parenterally transmittable hepatotropic RNA virus that causes acute and chronic hepatitis (80-90%) and hepatocellular carcinoma (10-15%). The mechanisms that determine the outcome of HCV infection are not well understood, although it is widely assumed that cellular immune response play an important role [1, 9].

Prevalence of HCV in the population of blood donors in Georgia has been investigated. Out of 4970 donors 7,3% had anti-HCV. Prevalence of HCV in Georgia is higher than national prevalence estimates of viral hepatitis in neighboring countries [2]. Viral factors associated with more rapidly progressive disease include high level viremia, genotype 1 and the degree of viral genetic diversity (quasispecies).

Cytokines are proteins and glycoproteins, which modulate the activity of target cells through binding to specific receptors. Cytokines can be classified either on

the basis of function, i.e. pro-inflammatory and anti-inflammatory cytokines or on the basis of whether they are produced principally by either Th-1 or Th-2 lymphocytes. Elimination of HC-virus significantly depends on the status of the balance between the two groups of cytokines [3-8].

The number of cytokines, chemokines and growth factors is ever-growing and it becomes increasingly evident that they are effective in a complex network of positive and negative signals. A disruption of this homeostatic balance is a direct cause of disease determines its complications and is related to its progression, e.g. inflammation and fibrogenesis. Cytokines are increasingly recognized as the important factors in the pathophysiology of chronic hepatitis C. Markers of cytokines expression at the early stage of the disease may be used as the criteria for prediction of further immune response.

Treatment of chronic hepatitis C is a prolonged process and very costly. In some cases the treatment is ineffective. Although the effectiveness of combination therapy with pegylated interferon- α and ribavirin

increased to almost 60-65%, there are still a lot of cases of non-responders and relapsers.

The early period of treatment of chronic HCV-infection has been studied to see if sustained response can be predicted. Early normalization of ALT level is a more accurate predictor of response to antiviral therapy than any of the other pretreatment factors. Dynamic changes of some cytokines during treatment may be used as a predictor factor for evaluation of the therapy effectiveness [3-8].

Materials and Methods

We have studied 92 Patients with chronic hepatitis C. Diagnosis was made using appropriate serological (anti-HCV ELISA), virological (HCV reverse transcription PCR), biochemical and histological criteria. HCV genotype (by the sequencing-based methodology) and viral load (by the quantitative HCV-RNA PCR) were defined as well. Patients with chronic hepatitis B, HIV-infection, haemochromatosis, Wilson's disease, α 1-antitripsin deficiency, autoimmune hepatitis or other autoimmune disease were excluded from our study. Mean age of patients was 46 ± 5 years. 60 patients were males (65%), 32- females (35%). Control group consisted of 16 healthy volunteers.

The following scheme of treatment was used: pegylated α -interferon-2b ("Peg-Intron", Essex Pharma) 1,5 μ g/kg weekly s.c. for 48 weeks if the genotype was 1 and for 24 weeks if the genotype was 2 or 3 plus ribavirin twice a day orally ("Rebetol") 10 mg/kg if the genotype was 1 and fix 800 mg/d if the genotype was 2 or 3.

Cytokines (serum level) were determined by ELISA method (R&D Systems, Wiesbaden) before, during (6, 12, 24 weeks) and after the treatment.

We have studied changes of Th1 derived cytokines: TNF- α , IL-1 β , Th2 derived cytokine IL-6 and additionally proinflammatory cytokines IL-18, TGF β 1 concentrations in the blood sera. As it is shown in the *Tab.1*, their changes were statistically significant as early as after 6 weeks of treatment, especially IL-1 β , IL-6 and IL-18. This status did not change significantly after completion of the treatment.

Measuring values and correlating them with responses should bring very important information in assessing and monitoring patients with HCV during treatment.

Results and Discussion

Initial levels of this cytokines and changes after 6 weeks during the treatment (especially of IL-6, IL-18) should be predictors for sustained response in combination therapy with interferon- α and ribavirin.

As the most dominant fibrogenic cytokine-TGF β 1 is of considerable interest in relation to progression and fibrogenesis in HCV. The contributions of and to the degree of inflammatory and fibrotic activity in HCV were investigated and described [6, 8].

IL-18 named interferon- γ (inducing factor, is a cytokine synthesized by Kupffer cells and macrophages. A lot of studies provide significant evidence indicating that IL-18 plays a prominent role in liver injury. It is structurally related to IL-1 β . Our study shows a significant up-regulation of IL-18 in chronic HCV infection, suggesting a role of this cytokine in the chronic cellular immune response toward hepatocytes in the course of this disease. It is important to note that Interferon- α promotes anti-inflammatory effects via two cytokine families prominently involved in the liver pathology, namely TNF- α and IL-1. We show that in HCV patients Interferon- α reduces IL-18 concentration. We propose that this anti-inflammatory mechanism contributes to the treatment efficacy with Interferon- α .

A persistent Th1 response may cause a gradual accumulation of liver injury induced by cytotoxic T lymphocytes and macrophages. These macrophages should then express a range of cytokines such TNF- α , IL-1 β , TGF β 1, IL-6, IL-18 and some chemokines, which are responsible to the continuation of a Th1 response.

This study shows an association between IL-18 and TNF- α , IL-1 β production. The notable upregulation of IL-18 correlated to a significance increase of TNF- α and IL-6 and to a week upregulation of IL-1 β .

Acknowledgements

This work was supported by the DAAD (German Academic Exchange Service) and INTAS.

CYTOKINE	BASELINE LEVEL pg/ml	AFTER 6 WEEKS OF TREATMENT pg/ml	AFTER 12 WEEKS OF TREATMENT pg/ml	AFTER THE TREATMENT pg/ml	CONTROL pg/ml	STATISTICAL SIGNIFICANCE P
	I	II	III	IV	V	
IL-1 β	5,77 \pm 1,49	5,89 \pm 1,78	2,61 \pm 0,55	2,56 \pm 0,77	1,87 \pm 0,21	I-III p<0,05 I-IV p<0,05 I-V p<0,05
IL-6	12,89 \pm 2,02	8,25 \pm 11,14	7,67 \pm 1,34	7,21 \pm 2,10	6,46 \pm 1,55	I-II p<0,05 I-III p<0,05 I-IV p<0,05 I-V p<0,01
IL-18	110,2-19,3	62,5-13,1	52,4-15,4	49,3-12,8	24,2-9,7	I-II p<0,05 I-III p<0,01 I-IV p<0,001 I-V p<0,001
TNF- α	14,78 \pm 2,25	11,17 \pm 12,34	8,65 \pm 1,45	8,34 \pm 2,75	6.36 \pm 12.41	I-III p<0,05 I-IV p<0,05 I-V p<0,01
TGF β 1	162.4 \pm 11,8	134,2 \pm 13,2	87,37 \pm 11,8	81,92 \pm 12,2	62,2 \pm 10,9	I-III p<0,001 I-IV p<0,001 I-V p<0,001

Tab.1 Level of serum cytokines before, during and after the treatment.

References

1. Butsashvili M., Tsertsvadze T., McNuttLA., Kamkamidze G., Gvetadze R., Badridze N.: Prevalence of hepatitis B, hepatitis C, syphilis and HIV in Georgia blood donors //European Journal of Epidemiology, 2001, 17: 693-695.
2. Booth J-C., Grady J-O., Neuberger J.: Clinical guidelines on the management of hepatitis C //Gut, 2001, 49 (Suppl. I): i1-i21.
3. Lapinski TW.: The levels of IL-1 β , IL-2, IL-4, IL-6 and INF-gamma among patients with chronic hepatitis C treated with Interferon- α //Bocz Akad Med Bialimst, 2000, 45: 211-227.
4. Lapinski TW.: The levels of IL-1 β , IL-4 and IL-6 in the serum and the liver tissue of chronic HCV-infected patients //Arch Immunol Ther Exp, 2001, 49: 311-316.

5. McGuinness PH., Painter D., Davies S., McCaughan GW. Increases in intrahepatic CD68 positive cells, MAC387 positive cells and proinflammatory cytokines (particularly interleukin 18) in chronic hepatitis C infection. // *Gut*, 2000, 46:260-269.
6. Neuman MG., Benhamou JP., Bourliere M., Ibrahim A., Malkiewicz IM., Asselah T., Martinot-Peignoux M., Shear NH.: Serum tumor necrosis factor-alpha and transforming growth factor-beta levels in chronic hepatitis C patients are immunomodulated by therapy // *Cytokine*, 2002, 17: 108-117
7. Oyanagy Y., Takahashi T., Matsui S., Takahashi S., Boku S., Takahashi K. Enhanced expression of Interleukin-6 in chronic hepatitis C. // *Liver*, 1999, 19: 464-472
8. Polyak SJ., Khabar KS., Rezeiq M., Gretch DR.: Elevated levels of interleukin-8 in serum are associated with hepatitis C virus infection and resistance to interferon therapy // *Journal of Virology*, 2001, 75: 6209-6211
9. Zakim D., Boyer Th. D.: *Hepatology: a textbook of liver disease*, 1998, (1568 pp)

Прогностическое значение некоторых цитокинов в развитии и терапии хронического гепатита С

*Гоча Барбакадзе, * Георгий Камкамидзе, * Вольфганг Штрелел**

- *Торакоабдоминальная клиника Тбилисской медицинской академии, Грузия;
**Отделение клинической иммунологии Центра реабилитации, Тбилиси, Грузия;
***Клиника внутренних болезней IV, Университет Гейдельберга, Германия

Р Е З Ю М Е

Течение и эффективность лечения гепатита С во многом зависит от особенностей клеточного иммунного ответа и продукции цитокинов, особенно проинфламаторных. Обследовано 92 больных с хроническим гепатитом С. В результате исследований обнаружено, что после 6 недель лечения пегилированным интерфероном альфа в комбинации с рибавирином концентрации сывороточных цитокинов IL-1 β , IL-6 и IL-18 изменились достоверно, а в конце лечения отмечалось достоверное снижение концентрации всех исследованных цитокинов.

Ключевые слова: *хронический гепатит С, цитокины, прогностические факторы*