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Original Article / Özgün Araştırma

Association of signal transducer and activator of transcription, interleukin-6, and interleukin-10 positivity with antiviral treatment in cirrhotic liver samples from patients with the hepatitis B or C virus

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Abstract

Objective: Terminal liver disease due to viral hepatitis infections is an important health problem. This study aimed to compare the expression of members of the signal transducer and activator of transcription (STAT) family (STAT-1, -2, -3, -5a, and -5b) and interleukin (IL)-6 and IL-10 in hepatectomy material from patients who received antiviral treatment and underwent a liver transplantation due to terminal liver failure.

Methods: The study consisted of 45 patients who underwent a liver transplantation due to chronic liver failure associated with viral hepatitis (hepatitis C virus [HCV] or hepatitis B virus [HBV]). The patients were divided into three groups according to the drug treatments they received prior to the liver transplantation: Group A: lamivudine, Group B: adefovir, and Group C: interferon or interferon + ribavirin.

Results: In the study population, 9 (20%) patients were females and 36 (80%) were males. The mean age was 45.7 (29–69) years. STAT-2, -3, and IL-6 expression were significantly higher in hepatocytes in Group A ($p<0.05$).

Conclusion: High STAT-3, high IL-6, and low STAT-1 expression were associated with optimum hepatocyte regeneration and liver metabolic function. In this regard, lamivudine was the most effective drug in the present study.

Keywords: STAT family, IL-6/ IL-10, nucleoside analogs, interferon, liver transplantation

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Hepatit B ve Hepatit C Nedenli Sirotik Karaciğer Metaryalinde Sinyal transdüserleri ve transkripsiyon aktivatörleri, İnterlökin-6, İnterlökin-10 Pozitifliğinin Antiviral Tedavi ile İlişkisi

Öz

Giriş: Viral hepatit infeksiyonlarına bağlı terminal dönem karaciğer hastalığı önemli bir sağlık sorunudur. Bu çalışmada antiviral tedavi almış terminal dönem karaciğer yetmezliği sebebiyle karaciğer nakli yapılan hepatektomi materyallerinde STAT-1,2,3,5,5a,5b, IL-6 ve IL-10 ekspresyonlarının karşılaştırılması amaçlandı.

Yöntemler: viral hepatitler (HCV ve HBV)'e bağlı kronik karaciğer yetmezliği nedeni ile karaciğer transplantasyonu yapılan 45 olgu çalışmaya dâhil edildi. Çalışmamızda hastalar karaciğer transplantasyonu öncesi almış oldukları ilaç tedavilerine göre 3 gruba ayrıldı. Grup A: Lamuvidine, Grup B: Adefovir, Grup C: İnterferon veya interferon + ribavidin.

Sonuçlar: Çalışma popülasyonunda 9 (%20) hasta kadındı ve 36 (%80) erkek idi. Yaş ortalaması 45.7 (29-69) idi. STAT-2, -3 ve IL-6 ekspresyonu Grup A'da hepatositlerde anlamlı olarak daha yüksekti ($p < 0.05$).

Sonuç: Yüksek STAT-3, yüksek IL-6 ve düşük STAT-1 ekspresyonu, optimumhepatositrejenerasyonu ve karaciğer metabolik fonksiyonu ile ilişkiliydi. Bu bağlamda, lamivudin, bu çalışmada en etkili ilaç olmuştur.

Anahtar kelimeler: STATs, IL-6, IL-10, Lamivudin, Adefovir, Ribavirin, Inerferon

INTRODUCTION

Terminal liver disease due to viral hepatitis infections is an important health problem, with approximately 500 million people reported to be infected with the hepatitis B virus (HBV)[1]. The prevalence of hepatitis C virus (HCV) infection is 2% and affects 200 million people[2]. Current treatment strategies for HBV and HCV include interferon (IFN)-alpha and the nucleoside analogs lamivudine and adefovir[3].

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway, which plays an important role in various cellular functions, is activated by more than 50 cytokines or growth factors in the human body[4]. JAKs are receptor-associated tyrosine kinases, which activate members of the STAT family STAT proteins have many functions, including antiviral defense in the liver and liver regeneration. They also provide protection against liver damage and ischemic perfusion damage. In the liver, interleukin-6 (IL-6) expression in hepatocytes stimulates the production of various acute phase reactants. IL-6 also plays an important role in liver regeneration and protecting the liver against injury[5]. IL-6 specifically induces STAT-3 activation and interleukin-10 (IL-10) plays a role in the activation of members of the STAT family[6].

This study aimed to compare the expression of STAT-1, -2, -3,-5a, and -5b, as well as that ofIL-6 and IL-10, in hepatectomy material from HBV and HCV patients with terminal liver failure who received different antiviral treatments before a liver transplantation.

METHODS

Study population

This study was carried out at the Department of general surgery. The study design was in accordance with the guidelines of the Declaration of Helsinki (Second revision, 2008) and was approved by the local ethics committee (İnonu University local ethics committee, 2008/20 grant number). The family was comprehensively informed prior to the procedure, and their written consent was obtained.

Forty-five patients who underwent a liver transplantation because of chronic liver failure due to viral hepatitis (HCV and HBV) were included in the study. Patients who were transplanted except viral hepatitis were excluded from the study. Demographic data on the patients, as well as their diagnoses and preoperative drug treatments, were recorded. The patients were divided into three groups according to the drug treatments they received prior to the liver transplantation: Group A (lamivudine), Group B (adefovir), and Group C (interferon or interferon + ribavirin). Each group consisted of 15 patients.

Liver Samples

The hepatectomy samples were examined immunohistochemically for STAT-1, -2, -3, -5, -5a, and-5b expression, in addition to IL-6 and IL-10 expression. Hepatocytes, bile duct epithelium, lymphocytes, and macrophages in the portal area, as well as Kupffer cells and fibroblasts in the stroma, were examined. Endothelial staining was also performed. Seven sections that were 5 mm thick were cut from right lobe parenchyma embedded in paraffin blocks, placed on Poly-L-Lysine-coated slides, and histopathologically examined in the department of pathology. The following STAT-1, -2, -3, -5a, and -5b and IL-6 and IL-10 primary antibodies (Ab) were used: rabbit polyclonal antibody (Ab) GTX26672 (GeneTex), IL-10 (rabbit polyclonal Ab, ab34843, Abcam), STAT-1 (rabbit polyclonal Ab, phospho S727, ab47754, Abcam), STAT-2 (rabbit polyclonal Ab, prediluted, ab31024, Abcam), STAT-3 (rabbit monoclonal Ab, 1122-1, Epitomics), STAT-5a (C-term) (rabbit monoclonal Ab, 1289-1, Epitomics), and STAT-5b (rabbit polyclonal Ab, phospho S731, ab52211, Abcam). All preparations to be stained by IL-6 were kept in an incubator at 60° C for 1 h. They were then rinsed in distilled water after being passed through xylol and alcohol, with gradual decreases in alcoholic strength.

Histopathological Study

The immunohistochemical examination was performed using the streptavidin-biotin peroxidase method and anti-polyvalent horseradish peroxidase (LabVision, Westinghouse, USA). The streptavidin-biotin method was applied as follows: The tissue sections were stained after treatment with 3% hydrogen peroxide for 8 min. The sections were then washed in phosphate buffered saline (PBS) solution. All the preparates were treated with Ultra V block for 10 mins. It was drained from the tissues without being washed, and the surrounding area was dried. The primary antibody was applied after dilution. The rates of dilution were 1/500 for IL-6, 1/400 for IL-10, 1/100 for STAT-1, 1/100 for STAT-3, 1/100 for STAT-5a, and 1/100 for STAT-5b. STAT-2 was available in a ready-to-use formulation. The application times were 70 min for IL-6, 75 min for IL-10, 90 min for STAT-1, 60 min for STAT-2, 60 min for STAT-3, 30 min for STAT-5, and 60 min for STAT-5b. The sections were then washed again with PBS. The sections were incubated with streptavidin peroxidase conjugate for 20 min and then washed with PBS. After the application of biotinylated secondary antibody for 20 min, they were washed again with PBS. The sections were ten incubated with the chromogen 3-amino-9-ethylcarbazole for 20 min. Subsequently, the sections were washed with deionized water and counterstained with Mayer's hematoxylin for 2–3 min, followed by washing with water. Glycerol gel was used as mounting medium, and the sections were covered with a cover slip.

All the procedures were carried out at ambient temperature in a humid environment to ensure that the sections did not become dry. The prepared sections were evaluated under a light microscope. Cells that stained positive for STAT proteins and IL-6 and IL-10 were detected. The nuclear staining method was used for grading of STAT staining. Cytoplasmic staining of IL-6 and IL-10 was also conducted.

Immunoreactivity in 10 different areas was examined using a light microscope, and the mean percentage of positively stained hepatocytes was scored.

Study Protocol

Protein expression in the liver was classified according to the following scale:

Grade 0 (G0): negative and staining in less than 10% of hepatocytes

Grade 1 (G1): 10–50% of positive hepatocytes

Grade 2 (G2): 51–75% of positive hepatocytes

Grade 3 (G3): staining in more than 75% of positive hepatocytes

Statistical Analysis

The statistical analysis was performed using SPSS 20.0 software (SPSS for Windows, Chicago, IL, USA). Spearman's rank correlation test was used to compare STAT protein expression and IL expression in the different groups, and $p<0.05$ was accepted as statistically significant.

RESULTS

In the study group, 9 (20%) patients were females, and 36 (80%) were males. The mean age was 45.7 (29–69) years. In terms of STAT-1 expression, in Group A, it was classified as G0 in 13 (86%) patients and G1 in 2 (14%) patients. In Group B, STAT-1 expression was classified as G0 in 13 (86%) patients, G1 in 1 patient (7%), and G2 in 1 patient (7%). No expression was classified as G3. In Group C, STAT-1 expression was classified as G0 in 13 (86%) patients and G1 in 2 (14%) patients. There was no statistically significant difference in STAT-1 expression between any of the groups ($p>0.05$).

STAT-2 expression was classified as G2 in 2 (14%) patients in Group A, and it was classified as G3 in 13 (86%) patients. In Group B, STAT-2 expression was classified as G1 in 6 (40%) patients, G2 in 3 (20%) patients and G3 in 6 (40%) patients. In Group C, STAT-2 expression was classified as G0 in 12 (80%) patients and G2 in 3 (20%) patients. There was a statistically significant difference in STAT-2 expression in the different groups ($p<0.05$).

With regard to STAT-3 expression, in Group A, it was classified as G2 in 4 (26%) patients and G3 in 11 (74%) patients. In Group B, it was classified as G0 in 14 (93%) patients and G1 in 1 (7%) patient. In Group C, it was classified as G0 in 12 (80%) patients, G1 in 1 (5%) patient and G2 in 3 (15%) patients (Figure1). There was a statistically significant difference in STAT-3 expression in in hepatocytes and lymphocytes of Group A as compared to that of the other groups ($p<0.05$).

In Group A, STAT-5a expression was classified as G0 in 13 (86%) patients and G1 in 2 (14%) patients. In Group B, it was classified as G0 in 5 (33%) patients, G1 in 6 (40%) patients and G2 in 4 (17%) patients. In Group C, it was classified as G0 in 2 (13%) patients, G1 in 1 (7%) patient, G2 in 3 (20%) patients, and G3 in 9 (60%) patients. There was a statistically significantly increase in STAT-5a expression in hepatocytes and lymphocytes of Group C as compared to that of the other groups ($p<0.05$). Both hepatocytes and lymphocytes expressed STAT-5a, and higher numbers of lymphocytes were stained with STAT-5a in Group C as compared to the other groups.

In Group A, STAT-5b expression was classified as G1 in 2 (14%) patients, G2 in 8 (53%) patients and G3 in 5 (33%) patients. In Group B, it was classified as G1 in 2 (14%) patients, G2 in 7 (46%) patients and G3 in 6 (40%) patients. In Group C, it was classified as G1 in 3 (20%) patients, G2 in 8 (53%) patients and G3 in 4 (27%) patients. There was no statistically significant difference in STAT-5b expression in the groups ($p>0.05$). Nuclear staining of STAT-5b was detected in biliary epithelium and lymphocytes, as well as in hepatocytes (Table).

Both IL-6 and IL-10 expression were detected in cytoplasm and some lymphocytes and

hepatocytes. IL-6 expression was classified as G3 in Group A and G1 in the other groups. IL-10 was classified as G2 in Group A and Group B and as G1 in Group 3(Figure2).

The expression of STAT-2, -3, and IL-6 was significantly higher in hepatocytes in Group A ($p<0.05$). There was a significant difference in STAT-2 expression in Group B versus that in Group C but no between-group difference in STAT-3 and IL-6 expression. STAT-5a expression showed an inverse relationship with STAT-2 expression, with the highest expression detected in Group C and the lowest expression found in Group B. STAT-1 and STAT-5a were weakly expressed in all the groups, and there was no significant difference in STAT-1 and STAT-5a expression in any of the groups. STAT-5b expression was high in all the groups, with no significant difference between any of the groups. IL-10 expression was lowest in Group C, and IL-10 expression in Group B was not significantly different from that in Group A.

Table1. STAT expression in the different groups.

	Group A (Lamivudine)				**Group B (Adefovir)**				**Group C (inf/ribavirin)**				***P value***
	Go	**G1**	**G2**	**G3**	**Go**	**G1**	**G2**	**G3**	**Go**	**G1**	**G2**	**G3**	
STAT1	13	2	0	0	13	1	1	0	13	2	0	0	>0.05
STAT2	0	0	2	13	0	6	3	6	12	0	3	0	**<0.05**
STAT3	0	0	4	11	14	1	0	0	12	1	3	0	**<0.05**
STAT5a	13	2	0	0	5	6	4	0	2	1	3	9	**<0.05**
STAT5b	0	2	8	5	0	2	7	6	0	3	8	4	>0.05

DISCUSSION

Liver cirrhosis continues to be a growing health problem worldwide. The main causes of liver cirrhosis are HBV, HCV, alcohol use, nonalcoholic steatohepatitis, and hereditary metabolic defects[7]. In Turkey and the rest of the world, HBV and HCV are the main cause of terminal-stage liver diseases[8]. It is estimated that over 350 million people worldwide are chronically infected with HBV and that about 600 thousand people die annually from HBV[8].

At present, IFN-α and nucleoside analogs, including lamivudine, entecavir, telbivudine, emtricitabine, tenofovir, and adefovir, are used as treatment for chronic viral hepatitis[9,10]. Only subgroups of patients are treated with IFN-α is being eradicated for a long time. Patients with a particularly high viral load rarely respond to IFN therapy. The efficacy of combination treatment with IFN and nucleoside analogs is unclear, with some controversial findings published[11,12]. The development of viral resistance and post-treatment relapse are frequently associated with fatal hepatic failure[13]. Therefore, new strategies are needed for the treatment of chronic viral hepatitis.

In liver, STAT-3 is primarily activated by IL-6, although IL-10 has also been reported to activate STAT-3[6]. STAT-3 has various functions. For example, Broomberg et al. demonstrated that it functioned as an oncogene[14]. STAT-3 was responsible for activation of the HBV regulator gene, which is normally activated by cytokines, such as epidermal growth factors or IL-6[15]. Furthermore, STAT-3 plays an important role

in antiapoptotic processes, glucose homeostasis, and fat metabolism through hepatocyte preservation, liver regeneration, and glucose homeostasis. IL-6 plays a protective role in chronic liver pathologies[5]. IL-6 has a wide protective role in chronic liver pathologies. Cytokine mediated STAT 3 activation in acute and chronic hepatitis is significant in HBV infection; because these activities limit the onset of liver diseases[16]. In this study, the expression of STAT-2, STAT-3, and IL-6 was significantly higher in hepatocytes in the lamivudine group (Group A).

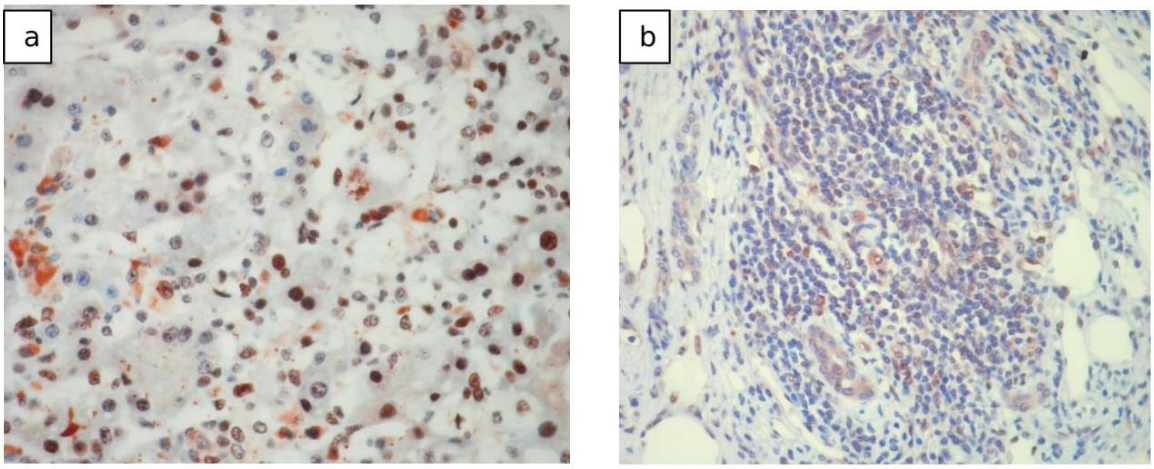

Figure1: The Grade 3 STAT3 expression (a) and STAT3 expression were found in lymphocytes apart from hepatocytes in group A (b).

As shown in previous research, after a liver transplantation, STAT-3 activation stimulates liver regeneration, whereas STAT-1 activation delays liver repair[6]. In this study, there was no statistically significant difference in STAT-1 expression in any of the treatment groups. Previous research showed that the development of fibrosis was characterized by a steady decrease in STAT-3 DNA-binding activity[17]. Studies also demonstrated that decreased STAT-3 activity in HCV was correlated with a reduction in hepatocyte proliferation and a decrease in the antiapoptotic balance of infiltrative inflammatory cells known as cell damage mediators[18,19]. In liver biopsies, HCV was correlated with the duration of chronicity and overexpression of STAT-1, -2, and 5 in chronic liver disease[16]. Expression of STAT-5 and STAT-3 in inflammatory cells was correlated with liver damage and inflammation[7]. In the present study, expression of STAT-3, STAT-5a, and STAT-5b was detected in lymphocytes. The number of lymphocytes stained with STAT-5a was highest in Group C, whereas the number of lymphocytes stained with STAT-3 was lowest in this group.

Previous studies showed that IL-6 inhibited cell cycle progression at the G0/G1 phase that it played a role in vivo in the function and proliferation of hepatocytes[20]. In the present study, patients with cirrhotic liver disease in the lamivudine treatment group showed the best outcomes in terms of hepatocyte regeneration and liver metabolic function, with a high MELD (Model for End-stage Liver Disease) score, high STAT-3 and IL-6 expression, and low STAT-1 expression.

Yilmaz et al. investigated hepatocyte proliferation in rats treated with lamivudine or adefovir following a partial hepatectomy and reported that the hepatocyte regeneration index was higher in the adefovir-treated group[21]. This result was not correlated with the positive effect of STAT and IL on liver regeneration in the cirrhotic liver in the present study. The discord in the findings may be due to the duration of treatment or liver status at the time the study was conducted. The study by Yilmaz et al. consisted of healthy medicated rats that underwent a partial hepatectomy. However, in the present study, the drug was administered to the cirrhotic liver. The different results might be related to this. Lamivudine may be more effective in cases of chronic liver damage. However, further studies are needed to confirm this idea.

STAT-5, particularly STAT-5b, plays a role in the activation of T-cell regulation[22]. STAT-5b defects are characterized not only by impaired growth but also immunological dysfunction[17]. STAT-5 deletion from hepatocytes results in aberrant activation of both STAT-1 and STAT-3[17,22]. In the present study, the low expression of STAT 1 in all the groups was inversely correlated with aberrant activation of STAT-5b. In contrast to IFN and Adefovir, STAT3 was found to be active with lamivudine. This result supports the effect of lamivudine and the activation of STAT-3 in response to elevated expression of IL6. Based on the findings of the present study, STAT-1 inhibition and possibly aberrant activation of STAT-5b appears to play an important role in treatment failure and attenuation of cirrhosis.

In conclusion, increased expression of STAT-5 and decreased expression of STAT-1 in all the patients in the present study suggests that these drugs are related to the fact that they have not been successful in the treatment of these patients in a process that culminates in cirrhosis. Its effects on the antiviral defense system and the results of IL-6 and STAT-1 indicate that none of the drugs were effective or superior to each other.The best effect in hepatocyte regeneration and metabolism was associated with high STAT 3, IL-6 expression and low STAT 1 expression, and in our study, lamivudine was found to be the most effective drug in this regard.

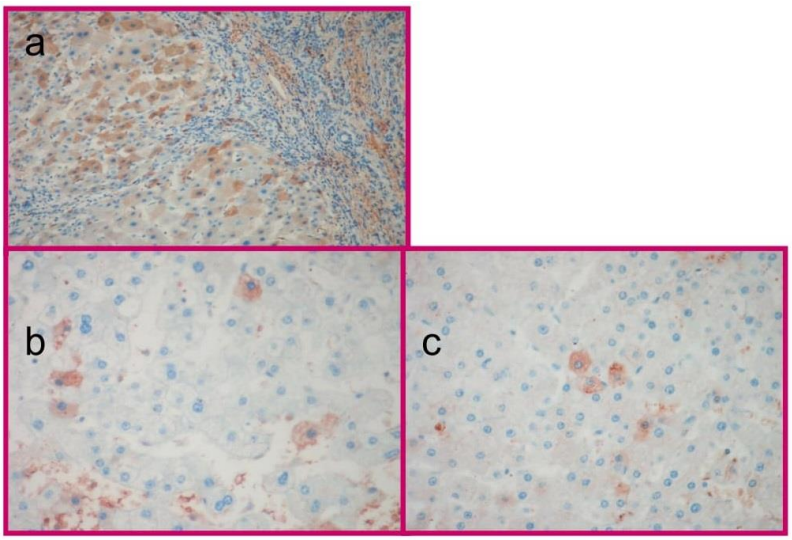

Figure2: IL-6 expression was present in cytoplasm in hepatocytes and was determined to be most intense in group A (a), it was observed at similar intensities in group B (b) and C (c).

Compliance with ethical standards

Ethical approval: The study design was in accordance with the guidelines of the Declaration of Helsinki (Second revision, 2008) and was approved by the local ethics committee.

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Conflict of interest: The authors declare no conflicts of interest.

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