Original Article

The role of interleukins in the progression of liver fibrosis in patients with chronic hepatitis c

Iskakova Aigerim Nabievna[1], Astrakhanov Akezhan Rustemuly[2], Nurlanova Gulzhanat Nurlanovna[1], Kurmangazin Meyrambek Sagnaevich[1], Kamzina Zauresh[3], Baubekova Asel[4], Donayeva Ainur[1], Rysbekova Gulsim[3], Bekova Nurgul[5], Zhenisbek Baubekov[1]

ABSTRACT

Chronic hepatitis C (CHC) remains a major global health burden, affecting approximately 58 million people worldwide and causing nearly 400,000 deaths annually due to complications such as cirrhosis and hepatocellular carcinoma (HCC). According to the World Health Organization. Progressive liver fibrosis is a central mechanism leading to these adverse outcomes and significantly reduces patients' quality of life. Interleukins play a crucial role in the inflammatory and fibrogenic processes associated with HCV infection. Pro-inflammatory cytokines, including IL-6, IL-1β, and TNF-α, contribute to hepatic stellate cell activation and collagen deposition, promoting fibrosis progression. Elevated levels of these cytokines have been shown to correlate with fibrosis severity. Recent studies also highlight the role of IL-33, IL-17, IL-25, and IL-1α as potential biomarkers of liver damage. Understanding cytokine-mediated mechanisms of fibrogenesis may improve early diagnosis, prognosis, and targeted therapeutic strategies in CHC patients.

Keywords

interleukins; liver fibrosis; chronic hepatitis C; inflammatory mediators; diagnostics; forecasting.

INTRODUCTION

Chronic hepatitis C (CHC) remains a major global public health concern, affecting millions of people worldwide. According to the World Health Organization, an estimated 58 million individuals were living with hepatitis C virus (HCV) infection in 2020. Each year, nearly 400,000 deaths are attributed to chronic hepatitis C, most often due to serious complications such as cirrhosis and hepatocellular carcinoma (HCC).

The natural progression of HCV infection frequently leads to liver fibrosis and, eventually, cirrhosis. These changes not only reduce patients' quality of life but also significantly increase the risk of developing liver cancer. Given these serious consequences, a deeper understanding of the mechanisms that drive liver fibrogenesis is essential for improving early diagnosis, preventing disease progression, and developing more effective therapeutic strategies [1].

Interleukins are key mediators of the inflammatory response and play an important role in fibrogenesis processes. In particular, interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) are actively

1. West Kazakhstan Marat Ospanov Medical University.
2. Infectious disease specialist of the Aktobe Regional Hepatology Center.
3. Kazakh-Russian Medical University.
4. Medical Astana University, Kazakhstan.
5. West Kazakhstan Medical University named after Marat Ospanov, Aktobe, Republic of Kazakhstan.

Correspondence
Baubekova Asel, Medical Astana University, Kazakhstan,
E-mail: b.asselya.sh@gmail.com

Bangladesh Journal of Medical Science Vol. 25 No. 02 April'26

DOI: https://doi.org/10.3329/bjms.v25i2.88745

involved in inflammatory processes, contributing to the activation of hepatic stellate cells and subsequent collagen deposition [2]. This is supported by studies showing that the levels of these cytokines correlate with the severity of fibrosis in patients with CFS [3,4].

Current studies confirm the significance of interleukins in the progression of liver fibrosis. For example, in a study by Askoura et al. (2022, it was found that the levels of interleukins IL-33, IL-17 and IL-25 correlate with the severity of fibrosis and can serve as biomarkers for assessing the degree of liver damage [5]. Similar results were obtained in another study, Tawfik et al. (2018), where it was shown that IL-1a levels are associated with inflammatory processes and fibrogenesis in patients with HCV [6].

The study of the role of interleukins in the pathogenesis of liver fibrosis is of great clinical importance, as it allows for improved diagnosis and prediction of disease progression. The inclusion of interleukin levels in clinical protocols can help identify patients at high risk of rapid progression of fibrosis, which in turn allows for more effective planning of therapeutic interventions.

MATERIALS AND METHODS

Therefore, the study of the role of interleukins in the progression of liver fibrosis in patients with CFS is an important and promising area of research. Understanding these mechanisms can contribute to the development of new diagnostic and therapeutic strategies aimed at improving the prognosis and quality of life for patients. Further research should focus on a more detailed study of the interactions between different cytokines and their effects on fibrogenesis, which will enable the creation of more accurate and effective methods for the diagnosis and treatment of HCV.

The aim of the study is to evaluate the impact of interleukin levels (Interleukin-1b, interleukin-6, interleukin-10, and tumor necrosis factor (TNF)) on the progression of liver fibrosis in patients with chronic hepatitis C.

Materials and methods of the study: The examination of 105 patients who had not previously received antiviral therapy (48 men and 57 women) with CHC in the reactivation phase was conducted at the Aktobe Regional Hepatology Center. The average age of the patients was 46.8±11.8 years, and the duration of infection was 2.65±1.8 years. All patients gave informed consent to participate in the study.

The analysis protocol was approved by the local ethics committee of the Marat Ospanov West Kazakhstan Medical University, protocol No. 58 dated January 17, 2020.

The diagnosis was established taking into account clinical, epidemiological and laboratory data, verified by the detection of HCV serological markers: detection of total antibodies of classes G and M to hepatitis C virus (HCV) by enzyme immunoassay (ELISA) on a Stat-Fax-2100 photometer using the Best anti-HCV kits (kit 2) and "Best anti-HCV" (kit 4) of JSC "Vector-Best", as well as the detection of class M antibodies to HCV using the kit "Recombi Best anti-HCV-IgM" JSC "VectorBest" (Novosibirsk). Ribonucleic acid (RNA) HCV was detected by polymerase chain reaction (PCR) on the Real-time "CFX-96" Bio-Rad Laboratories, Inc. (USA) using the "Real Best HCV" PCR kit (set 2) from ZAO "Vector-Best".

The Real Best Delta Mag HBV/HCV/HIV kit (kit 2, variant 2–8) was used to isolate HCV RNA from blood plasma for subsequent real-time PCR analysis. The sensitivity (detection limit) of the Real Best HCV PCR kit (kit 2) is as follows: in 100% of samples, HCV RNA is detected at a concentration of at least 15 IU/ml when RNA is isolated from 1 ml of sample (in the sample), which meets the international criteria for the recommended sensitivity of the method [9]. Virus genotyping was performed using the Real Best HCV RNA Genotype kit for the detection, quantitative analysis, and differentiation of the 1st to 3rd HCV RNA genotypes by reverse transcriptase PCR in real time (Vector-Best, Novosibirsk).

53 (50%) of 50 patients had the 1st genotype, 25 (24%) had the 2nd genotype, and 27 (26%) had the 3rd genotype.

Levels of TNF-α, IL-1β, IL-6, and IL-10 were determined by ELISA using the corresponding kits of ZAO Vector-Best and a Stat-Fax2100 plate photometer (USA). The stage of liver fibrosis was assessed by fibroelastography (FEG) before and after treatment, with measurement of the elasticity index (in kPa) and assessment of the fibrosis stage according to the METAVIR scale. Currently, there are no generally accepted threshold values for the elasticity index of the liver to differentiate the stages of fibrosis. For the group of patients with HCV, threshold values on the

METAVIR scale were used. The liver elasticity index with PH < 5.8 kPa indicates the absence of fibrosis (stage F0); 5.8–7.1 kPa corresponds to stage I fibrosis (F1); 7.2–9.5 kPa – stage II (F2); 9.6–12.5 kPa – stage III (F3); ≥ 12.5 kPa – cirrhosis of the liver (F4).

From the first day of the study, all patients were prescribed combination therapy for 12 weeks using the antiviral agent sofosbuvir 400mg + daclatasvir 60mg (SOF+ DCV) in accordance with the protocol of diagnosis and treatment of the Ministry of Health of the Republic of Kazakhstan No. 6 dated May 5, 2014.

The sustained virological effect was assessed 6 months after the completion of PVT.

The study was controlled by a specialist with a medical degree in the following study control points: before PVT, at 4, 12 weeks of therapy and 24, 36 weeks after PVT.

Statistical analysis and visualization of the obtained data was carried out using the R 4.4.0 statistical computing environment (R Foundation for Statistical Computing, Vienna, Austria).

Quantitative indicators were evaluated for compliance with the normal distribution using the Shapiro-Wilk test (for the number of subjects under 50) or Kolmogorov-Smirnov test (for the number of subjects over 50).

Quantitative indicators having a normal distribution were described using arithmetic means (M) and standard deviations (SD), 95% confidence interval limits (95% CI).

In the absence of a normal distribution, quantitative data were described using the median (Me) and the lower and upper quartiles (Q1 – Q3).

Categorical data were described using absolute values and percentages.

The mean values and standard deviations were calculated for the interleukin levels and fibrosis stages.

Correlation analysis was used to assess the relationship between interleukin levels and fibrosis stages at 24 and 36 months. The Pearson correlation coefficient was used to assess the linear relationship between two variables. The coefficient ranges from -1 to 1, where values close to 1 indicate a strong positive relationship, values close to -1 indicate a strong negative relationship, and values close to 0 indicate no linear relationship.

Regression analysis was used to model the relationship between interleukin levels and fibrosis stages. The primary goal was to create a predictive model that could explain changes in fibrosis stage based on interleukin levels. A linear regression model estimates the relationship between one or more independent variables (in this case, the levels of interleukin) and a dependent variable (the stage of fibrosis). Linear regression assumes a linear relationship between the variables.

The results of the study

After 24 weeks of treatment, there was a statistically significant decrease in the degree of fibrosis compared to its degree before treatment ($p<0.001$), while after 36 weeks, there was a statistically significant increase in the severity of fibrosis, up to the development of cirrhosis in 6 (5.8%) patients ($p<0.001$). Table 1 shows the results of the analysis of liver fibrosis over time.

Table 1. Dynamics of liver fibrosis in the study cohort of patients

Hepatic fibrosis	Observation period		
	before treatment	24 weeks	36 weeks
no	19 (18,3%)	20 (19,2%)	19 (18,3%)
1 degree	36 (34,6%)	52 (50%)	36 (34,6%)
2 degree	25 (24%)	32 (30,8%)	25 (24%)
3 degree	24 (23,1%)	0 (0%)	18 (17,3%)
Cirrhosis	0 (0%)	0 (0%)	6 (5,8%)
p^1	–	**<0,001**	0,815
p^2	–	–	**<0,001**

Four weeks after the start of therapy, the concentration of interleukin-6 increased by 0.5 (-2.6; 5.4) pg/mL ($p=0.084$). 12 weeks after the start of treatment, there was a statistically significant increase in the concentration of this marker by 4.1 (1.8; 6.4) pg/ml compared to the baseline level and by 2.4 (0.2; 5) pg/ml compared to the level at 4 weeks ($p<0.001$). After 24 weeks, the concentration of interleukin-6 decreased by 1.2 (0.3; 2.4) pg/ml ($p<0.001$) compared to the previous observation period, while the level remained significantly higher than the baseline value ($p<0.001$).

Four weeks after the start of therapy, the concentration of interleukin-10 increased by 1.9 (-0.6; 4.4) pg/ml

(p<0.001). Twelve weeks after the start of treatment, there was a statistically significant increase in the concentration of this marker by 9.2 (6.3; 15.1) pg/ml compared to the baseline level and by 6.8 (3.8; 12.4) pg/ml compared to the level at 4 weeks (p<0.001). After 24 weeks of therapy, there was no statistically significant change in the concentration of interleukin-10 compared to the previous observation stage (p=0.248), and the concentration of the marker remained statistically significantly higher than the initial level (p<0.001).

There were no statistically significant changes in the concentration of TNF-α during the observation period.

Table 2. Changes in the concentration of interleukins in the study cohort of patients.

Observation period		Me (Q1-Q3)	Comparison with the interleukin-1b level			
			before treatment		at the previous stage	
			Δ	p	Δ	p
Il-1b	before treatment	10,2 (4,1; 14,8)	–	–	–	–
	4 weeks	10,3 (5,3; 14,3)	-0,1 (-4; 4)	0,867	–	–
	12 weeks	14,6 (10,9; 16,7)	4,2 (1; 7,8)	<0,001	4,2 (1,7; 6,7)	<0,001
	24 weeks	14 (10,1; 15,9)	4 (-0,2; 6,8)	<0,001	-0,1 (-2,2; 1)	0,202
Il-6	before treatment	7,2 (3,2; 9)	–	–	–	–
	4 weeks	8,5 (4,2; 11,6)	0,5 (-2,6; 5,4)	0,084	–	–
	12 weeks	10,8 (9,2; 12,4)	4,1 (1,8; 6,4)	<0,001	2,4 (0,2; 5)	<0,001
	24 weeks	10,4 (8,5; 11,3)	3,5 (0,2; 6,9)	<0,001	-1,2 (-2,4; -0,3)	<0,001
Il-10	before treatment	5,5 (2; 7,3)	–	–	–	–
	4 weeks	7,5 (4,2; 10,5)	1,9 (-0,6; 4,4)	<0,001	–	–
	12 weeks	16 (10,4; 19,2)	9,2 (6,3; 15,1)	<0,001	6,8 (3,8; 12,4)	<0,001
	24 weeks	16,5 (11,1; 19,4)	9,8 (6,2; 13,8)	<0,001	0,5 (-1,2; 2)	0,248
TNF-α	before treatment	8 (6; 9,9)	–	–	–	–
	4 weeks	8,1 (6; 9,5)	-0,1 (-0,4; 0,6)	0,658	–	–
	12 weeks	8 (6,3; 9)	0 (-0,6; 0,6)	0,532	0 (-0,5; 0,6)	0,836
	24 weeks	8 (6,1; 9)	0 (-0,6; 0,9)	0,942	0 (-0,4; 0,5)	0,891

Statistically significant association (log_2) of the concentration of interleukin 1b before treatment with the severity of liver fibrosis before treatment (OR=1.25 [95% CI: 0.91; 1.73], p=0.177) and at 24 weeks (OR=1.28 [95% CI: 0.92; 1.8], p=0.147) and 36 weeks (OR=1.25 [95% CI: 0.91; 1.73], p=0.164) after its onset was not detected. There was also no statistically significant association of interleukin-1b concentrations at 4, 12, and 24 weeks after the start of treatment with the severity of fibrosis at 24 weeks (OR=1.19 [95%

CI: 0.86; 1.66], p=0.289, 1.51 [95% CI: 0.73; 3.19], p=0.267, and 1.91 [95% CI: 0.97; 3.86], p=0.065, respectively) and 36 weeks (OR=1.13 [95% CI: 0.83; 1.56], p=0.435, 1.36 [95% CI: 0.67; 2.76], p=0.391 and 1.48 [95% CI: 0.76; 2.89], p=0.248, respectively).

Ethical clearence

This study was conducted in accordance with ethical standards. Ethical approval was obtained from the appropriate institutional review board, and informed consent was secured from all participants prior to data collection.

RESULTS AND DISCUSSION

There was no statistically significant association (log_2) of the concentration of interleukin-1b before the start of therapy with a decrease in liver fibrosis after 24 weeks of treatment compared with baseline (OR=0.96 [95% CI: 0.67; 1.38], p=0.845) in the group of patients who had a decrease in liver fibrosis The median concentration of interleukin-1b was 9.3 (4.2; 13.5) pg/ml, in patients without decreased fibrosis – 9.9 (3.9; 15) pg/ml. There was no statistically significant association of interleukin-1b concentration with a decrease in liver fibrosis after 36 weeks compared with baseline (OR=0.77 [95% CI: 0.48; 1.21], p=0.253), in the group of patients who had a decrease in fibrosis severity after 36 weeks, the median concentration of interleukin-1b It was 7.6 (3.2; 12.6) pg/ml, in patients without a decrease in the severity of fibrosis -9.8 (4.2; 14.9) pg/ml.

Statistically significant association (log_2) of interleukin-6 concentration before treatment with the severity of liver fibrosis before treatment (OR=0.85 [95% CI: 0.64; 1.13], p=0.27) and at 24 weeks (OR=1.03 [95% CI: 0.76; 1.39], p=0.871) and 36 weeks (OR=0.87 [95% CI: 0.66; 1.15], p=0.315) after its onset was not detected. There was also no statistically significant association between the concentration of interleukin-6 at 4 and 12 weeks after the start of treatment and the severity of fibrosis at 24 weeks (1.17 [95% CI: 0.85; 1.62], p=0.341 and 1.24 [95% CI: 0.52; 2.96], p=0.631, respectively) and 36 weeks(OR=1.11 [95% CI: 0.81; 1.54], p=0.506 and 0.92 [95% CI: 0.4; 2.14], p=0.848, respectively). A 2-fold increase in interleukin-6 concentration 24 weeks after treatment initiation was statistically significantly associated with an increased odds of more severe liver fibrosis by an average of 4.34 [95% CI: 1.92; 10.3] at 24 weeks (p<0.001, Figure 39) and 2.97 [95% CI: 1.39; 6.54] at 36 weeks (p=0.006).

A 2-fold increase in the concentration of interleukin-6 before the start of therapy was a statistically significant predictor of a decrease in the chances of a decrease in the severity of liver fibrosis by an average of 1.7 [95% CI: 1.19; 2.56] times (p=0.007, Figure 1), in the group of patients with a decrease in the severity of liver fibrosis, the median concentration of interleukin-6 It was 5.2 (2.7; 7.6) pg/ml, in patients without decreased fibrosis severity – 7.1 (4.7; 11.1) pg/ml. There was no statistically significant association of interleukin-6 concentration with a decrease in liver fibrosis after 36 weeks compared with baseline (OR=0.93 [95% CI: 0.64; 1.39, p=0.714), in the group of patients who had a decrease in fibrosis severity after 36 weeks, the median concentration of interleukin-6 was 5.7 (2.8; 8.3) pg/ml, in patients without decreased fibrosis severity – 6.1 (3.2; 9.4) pg/ml.

Statistically significant association (log_2) of interleukin-10 concentration before treatment with the severity of liver fibrosis before treatment (OR=0.93 [95% CI: 0.74; 1.16], p=0.502) and at 24 weeks (OR=0.86 [95% CI: 0.68; 1.08], p=0.197) and 36 weeks (OR=0.93 [95% CI: 0.75; 1.16], p=0.536) after its onset was not detected. There was no statistically significant association of interleukin-10 concentrations at 4, 12, and 24 weeks after the start of treatment with the severity of fibrosis at 24 weeks (OR=1.06 [95% CI: 0.93; 1.24], p=0.41, 1.15 [95% CI: 0.65; 2.07], p=0.627, and 1.48 [95% CI: 0.8; 2.77], p=0.215, respectively). There was also no statistically significant association between the level of interleukin-10 at 4 and 12 weeks and the severity of fibrosis at 36 weeks after the start of therapy (OR=1.07 [95% CI: 0.94; 1.25], p=0.289 and 1.42 [95% CI: 0.83; 2.49], p=0.21, respectively).

10, 24 weeks after the start of treatment, was associated with an increase in the severity of liver fibrosis at 36 weeks by an average of 1.82 [95% CI: 1.02; 3.31] times (p=0.045).

There was no statistically significant association of interleukin-10 concentration with a decrease in liver fibrosis after 24 weeks compared with baseline (OR=0.95 [95% CI: 1.2; 0.74], p=0.652), in the group of patients who had a decrease in fibrosis severity after 24 weeks, the median concentration of interleukin-10 It was 3.5 (2; 10.4) pg/ml, in patients without a decrease in the severity of fibrosis – 3.7 (2; 5.3) pg/ml. There was also no statistically significant association of interleukin-10 concentration with a decrease in

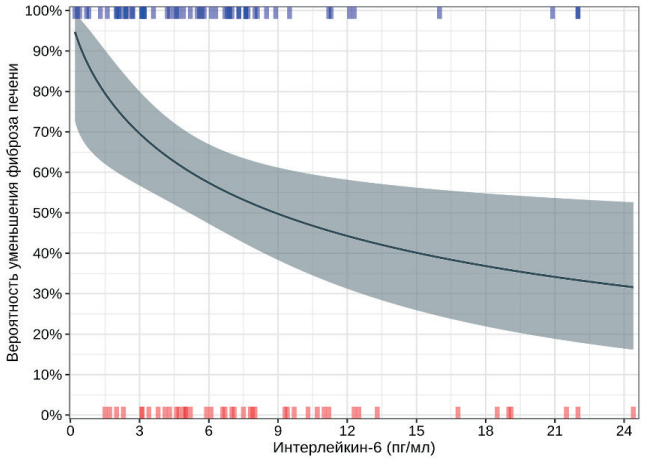

Figure 1. Probability of reducing the severity of liver fibrosis after 24 weeks, depending on the level of interleukin-6 before therapy.

liver fibrosis after 36 weeks compared with baseline (OR=1.05 [95% CI: 0.78; 1.45], p=0.768), in the group of patients who had a decrease in fibrosis severity after 36 weeks, the median interleukin concentration was10 was 3.5 (2.9; 5.6) pg/ml, in patients without decreased fibrosis severity – 3.7 (2; 7.3) pg/ml

Statistically significant association (log_2) of TNF-α concentration before treatment with the severity of liver fibrosis before treatment (OR=0.87 [95% CI: 0.44; 1.7], p=0.68) and at 24 weeks (OR=0.96 [95% CI: 0.47; 1.97], p=0.904) and 36 weeks (OR=0.9 [95% CI: 0.46; 1.78], p=0.768) after its onset was not detected. There was no statistically significant association (log_2) of TNF-α concentrations at 4, 12, and 24 weeks after the start of treatment with the severity of fibrosis at 24 weeks (OR=1.04 [95% CI: 0.51; 2.1], p=0.919, 1.06 [95% CI: 0.49; 2.29], p=0.886 and 1.1 [95% CI: 0.48; 2.53], p=0.824, respectively) and 36 weeks (OR=1.03 [95% CI: 0.53; 2], p=0.928, 0.84 [95% CI: 0.41; 1.73], p=0.635 and 0.93 [95% CI: 0.42; 2.05], p=0.848, respectively).

A 2-fold increase in TNF-α concentration before treatment was statistically significantly associated with a decrease in the chances of a decrease in liver fibrosis severity after 24 weeks by an average of 2.49 [95% CI: 1.13; 5.8] times (p=0.028, Figure 2), in the group of patients who had a decrease in the severity of fibrosis after 24 weeks, the median TNF-α concentration was 6.8 (5.8; 8.3) pg/ml, in patients without a decrease in the severity of fibrosis – 8.1 (6.2; 11.4) pg/ml. There was also a tendency to have an inverse association between TNF-α levels before starting therapy with the likelihood of a decrease in liver fibrosis severity after 36 weeks: a 2-fold increase in the marker concentration was accompanied by a decrease in the chances of a decrease in fibrosis severity by an average of 2.55 [95% CI: 0.9; 8.03] times (p=0.089, Figure 3), in the group of patients who had a decrease in the severity of fibrosis after 36 weeks, the median TNF-α concentration was 6.4 (6; 7.3) pg/ml, in patients without a decrease in the severity of fibrosis – 7.7 (6; 11.1) pg/ml.

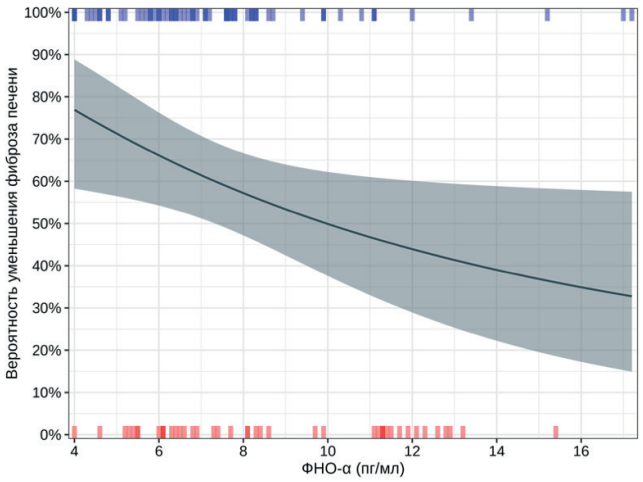

Figure 2. Probability of reducing the severity of liver fibrosis after 24 weeks, depending on the concentration of TNF-α before treatment.

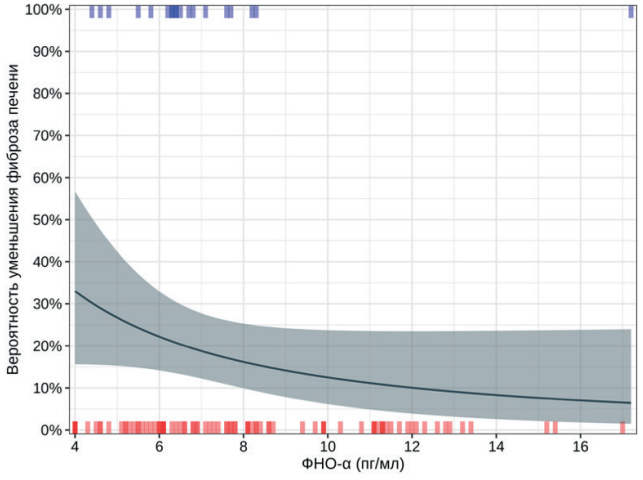

Figure 3. Probability of reducing the severity of liver fibrosis after 36 weeks, depending on the concentration of TNF-α before treatment.

Discussion of the results

This study examined the effect of interleukin levels, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α), on the progression of liver fibrosis in patients with chronic viral hepatitis C (CHC). The results are consistent with the findings of several other studies, confirming the key role of inflammatory mediators in the pathogenesis of liver fibrosis.

IL-6 is an important inflammatory mediator and immune response regulator that plays a central role in the pathogenesis of liver fibrosis. In our study, we found a significant increase in IL-6 levels in patients at 12 weeks of treatment, which correlated with an increase in the severity of fibrosis. This is consistent with the results presented in the study by Tanwar et al. (2020), where IL-6 was identified as one of the key markers of the inflammatory process leading to fibrosis in patients with chronic liver diseases, including CHD [8]. In this study, it was shown that IL-6 promotes the activation of liver stellate cells, stimulating the production of collagen and the development of fibrosis.

An increase in IL-6 levels is associated with the activation of inflammatory processes and may serve as a predictor of fibrosis progression. In particular, a study by Saraiva et al. (2018) showed that the elimination of the virus through sofosbuvir therapy leads to a decrease in the levels of inflammatory cytokines such as IL-6, indicating its important role in maintaining inflammation in viral hepatitis [10].

IL-10, with its powerful anti-inflammatory properties, can reduce the activity of pro-inflammatory cytokines such as IL-6 and play a protective role in liver fibrosis. Our data demonstrated a significant increase in IL-10 levels in patients after 12 weeks of therapy, which may indicate modulation of the inflammatory process in response to antiviral therapy. This is consistent with the results of a study presented by Tanwar et al. (2020), which showed that an increase in IL-10 levels is associated with improved inflammatory status and a reduced risk of fibrosis progression [8].

IL-10 inhibits the production of pro-inflammatory cytokines such as IL-6 and TNF-α, thereby reducing the activity of inflammatory processes that contribute to fibrogenesis. This is supported by the results of a study by Wang et al. (2018), where IL-10 was identified as a key factor in modulating the inflammatory response in chronic hepatitis and fibrosis [9].

Interleukin-1β (IL-1β) is a key pro-inflammatory cytokine involved in the activation of liver cells and the development of fibrosis. In our study, the level of IL-1β increased at the 12th week of treatment, which may indicate an increase in the inflammatory process at this stage. According to Tanwar et al. (2020), IL-1β is involved in the activation of liver stellate cells, stimulating them to produce collagen and develop fibrosis [8].

However, as our study showed, IL-1β levels stabilized by the 24th week of therapy, which may be related to the anti-inflammatory effect of the therapy, similar to the findings of the study by Saraiva et al. (2018), where sofosbuvir therapy contributed to the restoration of the balance of inflammatory mediators [10].

TNF-α, as a pro-inflammatory cytokine, plays an important role in the early activation of inflammatory processes and the stimulation of liver stellate cells. In our study, no significant changes in the level of TNF-α were observed during the course of therapy. This may suggest that at this stage of the disease, the role of TNF-α in the progression of fibrosis is weakening, as was also shown in the work of Wang et al. (2018), where TNF-α played a less significant role in the later stages of fibrosis [11].

CONCLUSION

In this study, it was found that the levels of interleukin cytokines such as IL-6, IL-1β, IL-10 and TNF-α play an important role in the progression of liver fibrosis in patients with chronic viral hepatitis C (CHC). Increased levels of IL-6 and IL-1β were correlated with increased inflammatory processes and activation of fibrogenesis, whereas an increase in IL-10 levels, on the contrary, indicated a decrease in inflammation and a slowdown in the progression of fibrosis.

The data confirm the importance of monitoring interleukin levels as potential biomarkers to help assess the risk of fibrosis progression and the effectiveness of anti-inflammatory and antiviral therapy in patients with CSC. Elevated levels of IL-6 and IL-1β may serve as an indicator of increased inflammation and fibrosis development, while increased IL-10 is associated with a favorable response to therapy.

Additional studies involving the analysis of other key cytokines, such as IL-17 and TGF-β, may contribute

to a deeper understanding of the mechanisms of fibrogenesis and help in the development of new therapeutic approaches. These findings also highlight the importance of a comprehensive approach to the treatment of chronic liver diseases, aimed at modulating inflammatory processes in order to prevent the development of fibrosis and cirrhosis.

Conflict of Interest: The author declare no conflict of interest.

Authors's contribution

Data gathering and idea owner of this study: Iskakova Aigerim, Astrakhanov Akezhan

Study design: Nurlanova Gulzhanat, Kurmangazin Meyrambek

Data gathering: Kamzina Zauresh, Baubekova Asel

Writing and submitting manuscript: Donayeva Ainur, Rysbekova Gulsim

Editing and approval of final draft: Bekova Nurgul, Zhenisbek Baubekov

REFERENCES

1. Brzdęk M, Dobrowolska K, Pabjan P, Zarębska-Michaluk D. Clinical characteristics and antiviral therapy in patients infected with hepatitis C virus in the interferon-free era. *Pol Arch Intern Med.* 2022 Jun 28;
2. Ganesan M, Poluektova L, Enweluzo C, Kharbanda K, Osna N. Hepatitis C Virus-Infected Apoptotic Hepatocytes Program Macrophages and Hepatic Stellate Cells for Liver Inflammation and Fibrosis Development: *Role of Ethanol as a Second Hit. Biomolecules*. 2018 Oct 13;**8**(4):113.
3. Costa D, Simbrunner B, Jachs M, Hartl L, Bauer D, Paternostro R, et al. Systemic inflammation increases across distinct stages of advanced chronic liver disease and correlates with decompensation and mortality. *J Hepatol*. 2021 Apr;**74**(4):819–28.
4. Sepulveda-Crespo D, Resino S, Martinez I. Strategies Targeting the Innate Immune Response for the Treatment of Hepatitis C Virus-Associated Liver Fibrosis. *Drugs.* 2021 Mar 5;**81**(4):419–43.
5. Askoura M, Abbas HA, Al Sadoun H, Abdulaal WH, Abu Lila AS, Almansour K, et al. Elevated Levels of IL-33, IL-17 and IL-25 Indicate the Progression from Chronicity to Hepatocellular Carcinoma in Hepatitis C Virus Patients. *Pathogens.* 2022 Jan 3;**11**(1):57.
6. Tawfik AK, Amin AM, Yousef M, El-sayd NM, Elashry HM, Elkadeem M, et al. IL-1α correlates with severity of hepatitis C virus-related liver diseases. *J Inflamm Res.* 2018 Jul;Volume **11**:289–95.
7. Assessment of interleukin 17 and transforming growth factor-beta 1 in hepatitis C patients with disease progression. *Trop Biomed*. 2020 Dec 30;**37**(4):1093–104.
8. Tanwar S, Rhodes F, Srivastava A, Trembling PM, Rosenberg WM. Inflammation and fibrosis in chronic liver diseases including non-alcoholic fatty liver disease and hepatitis C. *World J Gastroenterol.* 2020 Jan 14;**26**(2):109–33.
9. Wang YQ, Cao WJ, Gao YF, Ye J, Zou GZ. Serum interleukin-34 level can be an indicator of liver fibrosis in patients with chronic hepatitis B virus infection. *World J Gastroenterol*. 2018 Mar 28;**24**(12):1312–20.
10. Saraiva GN, Rosário NF do, Medeiros T, Leite PEC, Lacerda G de S, Andrade TG de, et al. Restoring Inflammatory Mediator Balance after Sofosbuvir-Induced Viral Clearance in Patients with Chronic Hepatitis C. *Mediators Inflamm*. 2018 May **27**;2018:1–12.
11. Fuadi, A. F. ., Riwanto, I. ., Putra, A. ., Prabowo, E. ., & Istiadi, H. . (2022). Mesenchymal Stem Cells Combined with Bovine Colostrum Decrease the PDGF and Fibrosis Level after Hepatectomy in Liver Fibrosis Rats Model. *Bangladesh Journal of Medical Science*, **21**(2), 262–270. https://doi.org/10.3329/bjms.v21i2.58057