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Evaluation of efficacy and safety of interferon-free "3D" regimen among patients with non-compensated cirrhosis caused by HCV genotype 1b infection

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ABSTRACT

Objective: The first interferon-free regimen became available in Russia in 2015. It brought hope to HCV Gt1 patients with cirrhosis for whom interferon-based schemes found to be non-effective or contraindicated. 3D therapy was the only available etiotropic option for them. New safety data published after the start of our study significantly limited usage of this regimen among patients with non-compensated cirrhosis. The aim of this study was to evaluate efficacy and safety of the 3D interferon-free regimen among HCV Gt1b patients with non-compensated cirrhosis.

Method: 66 patients (26 males and 40 females) with HCV Gt1b and non-compensated cirrhosis were enrolled. All of them were treated with ombitasvir/paritaprevir/ritonavir, dasabuvir and ribavirin for 12 weeks. Ribavirin was discontinued after 4 weeks of therapy due to onset of new data on the efficacy of 3D regimen without ribavirin in Turquoise III study published in September 2015 before the change of package insert. Child-Pugh score was assessed before the start of antiviral therapy as follows: 21 patients (31,8%) – 9 points, 11 patients (16,7%) – 8 points, 34 patients (51,5%) – 7 points. The key method used to evaluate study results was modified intent-to-treat (mITT) analysis because number of analyzed patients within treatment period changed after withdrawal caused by safety reasons but followed by assessment of efficacy among patients who discontinued treatment. Per protocol (PP) method was also used in addition to mITT.

Results: Aviremia after 14 days of treatment was reached among 35 out of 65 patients (53,8%), rapid virologic response – among 79,7% patients (51/64). Each patient who received full 12-week course of treatment (n=60) including those who discontinued due to safety reasons (n=3) between 14th and 30th days of therapy reached SVR12 and SVR24. Assessment of Child-Pugh score in 6 months after EOT demonstrated decrease by 3-4 points among 21 patients (33,9%) and by 1-2 points among 35 patients. 66,1% patients reached clinical improvement in MELD score. Treatment discontinuation was caused by progression of hepatic encephalopathy and/or jaundice (4 cases). Those adverse events regressed among majority of patients after discontinuation of therapy. 3 deaths were reported (bacterial endocarditis, progression of hepatic encephalopathy and bleeding from gastric ulcers) during treatment period and 1 death in follow-up period due to progression of hepatocellular carcinoma.

Conclusion: 3D therapy was effective in 100% patients (mITT) with HCV GT1b and non-compensated cirrhosis both among those who completed full therapy course and those who discontinued the therapy due to safety reasons. Safety analysis demonstrated that the rate of severe adverse events was comparable with natural course of HCV-infection in patients on non-compensated cirrhotic stage without antiviral treatment.

Keywords: chronic hepatitis C, genotype 1b, liver cirrhosis, treatment

INTRODUCTION

Chronic liver diseases, characterized by many years of asymptomatic progression, often cause early disability and mortality due to severe complications – liver cirrhosis and cancer. Currently the stable growth of these outcomes worldwide reflects massive spread of infection in the 2nd half of XX century. In many cases patients seeks for medical care on the stages of late disease complications. As a result, chronic viral liver diseases are often diagnosed on non-compensated cirrhotic stage.

Liver cirrhosis is one of the key factors deteriorating prognosis for patient's life (1, 2, 3). Risks of such outcomes as liver insufficiency, hepatocellular carcinoma (HCC) or death related to liver disease are 2,9%, 3,2% and 2,7% respectively (4, 5, 6). Cumulated data on natural history of HCV demonstrate that liver cirrhosis develops during 20 years among

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~16% of patients (7). Along with that, data on higher cumulated risk of cirrhosis among 15% of patients within 5 years of observation has been published (8, 9). Contradictions in such results should be underlined but broad clinical experience makes the last statement more convincing. The majority of patients with liver cirrhosis reach the age of 50-60 years when diagnosis is established (10, 11). It means that ignoring the impact of other systemic diseases on acceleration of liver fibrogenesis seems to be huge misbelief. Moreover, most frequent deterioration factors – alcohol abuse and metabolic disorders lead to fatty liver disease. Obviously, growing number of HCV-associated liver cirrhosis and complicated forms of liver diseases correspond to current aging of baby boomers generation (12, 13). Rising morbidity from HCC is another result of mentioned processes. Contrary to stable prognosis in liver cancer caused by HBV, increased frequency of HCC among patients with long history of HCV becomes a heavy social and economic burden on national level [14, 15]. Finally, need for liver transplantation grows in parallel and turns to heavy financial costs together with deficiency of donor organs in many countries (16, 17).

Interferon-based regimens were contraindicated for majority of patients in waiting lists for transplantation. These regimens could be used only for patients with Child-Turcotte-Pugh score ≤ 8 and MELD score < 16-17. The main goal of antiviral therapy for these patients was to reach SVR and elude recurrent infection after transplantation (18). Key limitations of this method were related to the high risk of severe adverse events and low probability of SVR. Nevertheless this only available option brought evident positive results, demonstrating increase of survival and decrease of HCC rate (19).

Hopes for rising efficacy brought by adding the 1st generation of protease inhibitors to standard IFN/RBV therapy were shaded by the results of post-marketing studies which had demonstrated deterioration of safety profile among patients with cirrhosis. CUPIC study results demonstrated that triple therapy often was not the best choice for such patients (20). Platelet count <103 cells/μL and albumin <3,5 g/dL determined minimal chances for cure with high probability of severe adverse events and liver failure. In these cases SVR ≤ 12% and risk of severe complications over 50% gave the treatment scheme no chance even as an alternative.

Introduction of all oral interferon-free regimens and advances in treatment approaches within the last years gave an opportunity to eliminate HCV infection worldwide. Brand new therapy concept, high efficacy, significant decrease of the role of such limiting factors as co-morbidity enabled to broaden indications for hard-to-treat category – patients with evolving cirrhosis as an outcome of long lasting HCV infection.

Registration of "3D" regimen (ombitasvir/paritaprevir/ritonavir, dasabuvir) in Russia in April 2015 and further opportunity to use this scheme without ribavirin was the only option to treat patients on the final stage of liver disease. It became the salvage therapy. Based on results of registration clinical studies, it demonstrated independence from old predictors for achieving SVR and superior safety profile on compensated cirrhosis stage. Currently it is recommended that 3D therapy should be avoided in patients with advanced liver disease. This fact was based on several reports on severe adverse events which led to death or necessity of urgent liver transplantation in patients with decompensated liver cirrhosis (21). On the other hand, absence of alternative treatment options for these patients provided pessimistic scenario in case of natural disease progression. In such a way clinical dilemma concerning necessity to treat patients with late stage cirrhosis (Child-Pugh B-C) is still an open question. Under such circumstances the choice between passive observation and start of therapy with 3D regimen was obvious.

MATERIALS AND METHODS

66 patients with non-compensated cirrhosis as a result of HCV Gt1b infection were enrolled for treatment with 3D regimen in September 2015. Child-Pugh score was assessed before the start of therapy as follows: 21 patients (31,8%) – 9 points, 11 patients (16,7%) – 8 points, 34 patients (51,5%) – 7 points. Decrease of albumin level, hyperbilirubinemia and hepatic encephalopathy were most impactful factors in the development of liver insufficiency.

Patients' pool consists of 26 males and 40 females, 36-68 years of age (**Table 1**). Patients received 2 tabs of ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg once a day and 1 tab of dasabuvir 250 mg twice a day. Additionally twice-daily dosing of ribavirin was administered at 1000 mg daily to the patients whose body weight was less than 75 kg and 1200 mg daily to thepatients whose body weight was 75 kg or greater. Therapy for all the patients started at the same time. Planned treatment duration was 12 weeks. In 4 weeks after the start of therapy ribavirin was discontinued based on TURQUOISE-III clinical study results (22), according to which the similar efficacy with better safety profile was achieved. Starting from week 5 all the enrolled patients continued therapy only with 3D regimen. Modified intent-to-treat (mITT) analysis was used to evaluate the efficacy. It included data on each patient who received at least 1 pill and who was eligible for the final assessment. On the principle of ITT analysis, preliminary withdrawal on any reason, absence

Table 1: *Baseline demographical and clinical characteristics*

Parameter		Number (%) of patients
Sex	Male	26 (39,4)
	Female	40 (60,6)
Age, years	< 50	17 (25,8)
	> 50	49 (74,2)
BMI, kg/m^2	< 25	20 (30,3)
	25-29,9	29 (43,9)
	≥30	17 (25,8)
IL28b genotype	CC	15 (22,7)
	CT	44 (66,7)
	TT	7 (10,6)
HCV RNA level, x10^6, IU/mL	< 0,8	57 (86,4)
	≥0,8	9 (13,6)
Child-Pugh score, points	7	34 (51,5)
	8	11 (16,7)
	9	21 (31,8)
Platelet count, x10^3 cells/μL	< 50	6 (9,1)
	50-75	13 (19,7)
	75-100	(16,7)
	> 100	36 (54,5)

or loss of data was interpreted as treatment failure. Moreover, per-protocol analysis was used additionally to estimate treatment efficacy among all patients who completed the full 12-week course. Therapy was provided within compulsory healthcare insurance funding. Monitoring of the efficacy and safety was assured by day patient facilities of clinics in Moscow Region.

Average observation period in Moscow Regional Hepatology Center from the moment of established diagnosis to the start of 3D therapy was 2,8±1,8 years. Cirrhosis was confirmed by clinical, laboratory and instrumental methods including liver elastography in absolute majority of patients. Average density of liver tissue at baseline was 38,4±17,1 kPa. Only 5 patients (7,6%) previously underwent liver biopsy. Primary cirrhosis on sub-compensation stage (Child-Pugh B – 7-9 points) associated with HCV was diagnosed in 42 (63,6%) patients. Minority of patients asked for specialized medical care due to compensated cirrhosis in the past. In our opinion, co-morbidities (alcoholic liver disease, hemochromatosis, autoimmune hepatitis, metabolic liver disorders caused by obesity and diabetes mellitus 2nd type), aggravated somatic conditions (chemotherapy in anamnesis, diabetes mellitus 2nd type, severe hypertension, psoriasis, ischemic heart disease), age (74,2% of patients elder than 50 years), inability to use antiviral therapy or/and inefficiency of previously used therapy caused progression of cirrhosis.

34 (51,5%) patients never received any antiviral therapy before. 5 patients previously used interferon-based therapy in LADR regimen due to inability to be treated with full dose schemes. Previously used standard double therapy was ineffective in 14 patients. The rest 13 patients received triple therapy with the 1st generation of protease inhibitors (boceprevir, telaprevir) before start of the interferon-free therapy. The reasons of treatment failures were: absence of virologic response in 43,9% cases, HCV relapse in 30,3% cases, virologic breakthrough in 16,7% cases and severe adverse events in 9,1% cases (**Table 2**).

Inability to reach compensation of liver function was the key factor limiting use of IFN-containing therapy before interferon-free regimens became available. More than half of patients had to stay for a period of time in full day clinic within 6 months before start of 3D therapy. The most often reasons for hospitalization were progression of hepatic encephalopathy (30,3%), ascites (16,7%) and bleeding from esophageal varices (9,1%). After preliminary examination esophageal varices were diagnosed among 74,2% patients, in 30,3% of them esophageal varices ligation was performed (**Table 2**).

RESULTS

Efficacy of 3D Therapy among Patients with Liver Cirrhosis

Considering severity of current status, it was decided to discontinue treatment in several patients due to development of adverse events potentially deteriorating the state of cirrhosis. Absence of HCV RNA after 14 days of treatment was reached among 35 out of 65 patients (53,8%), rapid virologic response – among 79,7% patients (51/64) (Figure 1). After 8 weeks of treatment HCV RNA was undetectable in all 62 patients who continued therapy. All of them had negative PCR test results. Those 3 patients who withdrawn therapy between 14 and 30 days after its start due to safety reasons

Table 2: *Baseline clinical characteristics*

Parameter		Number of patients, abs. (%)
Treatment history	Peg-IFN α + RBV	14 (21,2)
	Peg-IFN α + RBV + PI	13 (19,7)
	LADR	5 (7,6)
	No previous therapy	34 (51,5)
Response to previous therapy	Null-responder	29 (43,9)
	Relapser	20 (30,3)
	Virologic breakthrough	11 (16,7)
	Severe AE	6 (9,1)
Systemic co-morbidities	Obesity	12 (18,2)
	Arterial hypertension	10 (15,1)
	Diabetes mellitus 2nd type	7 (10,6)
	Ischemic heart disease	5 (7,6)
	Autoimmune hepatitis	2 (3,0)
	Cancer	2 (3,0)
	Psoriasis	2 (3,0)
	Chronic renal insufficiency	2 (3,0)
	Cryoglobulinemic vasculitis	1 (1,5)
Liver co-morbidities	Alcoholic liver disease	7 (10,6)
	NAFLD	6 (9,1)
	Genetic hemochromatosis	6 (9,1)
	Autoimmune hepatitis	2 (3,0)
Symptoms of portal hypertension	Esophageal varices 1-2 stage	37 (56,1)
	Esophageal varices 3 stage	12 (18,2)
	Hemorrhage in anamnesis	9 (13,6)
	Esophageal varices ligation	20 (30,3)
Inpatient admission during previous 6 months due to liver function deterioration	Ascites and hepatic encephalopathy	11 (16,7)
	Hepatic encephalopathy	20 (33,3)
	Esophageal varices hemorrhage	6 (9,1)

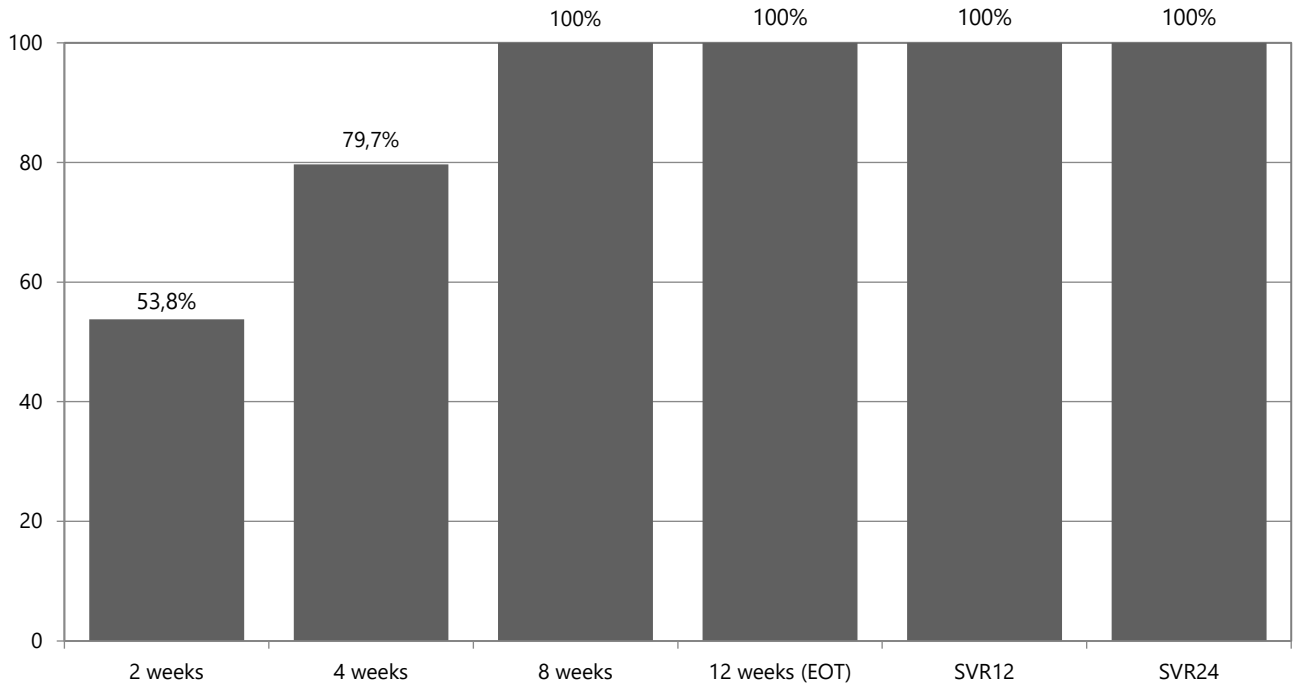

Figure 1: *Assessment of viral response on 3D regimen among patients with non-compensated cirrhosis (mITT analysis)*

continued to stay under observation with PCR control in standard timeframes. All of them achieved SVR12 and SVR24. Such results were astonishing especially taking into consideration the severe stage of disease – non-compensated cirrhosis and inability to use regular antiviral therapy beforehand. In summary, all patients who accomplished 12 weeks regimen (n=60) including those who withdrawn from therapy early before EOT (n=3), reached SVR12 and SVR24 (**Figure 1**).

According to Intention-to-treat (ITT) analysis, 93,9% patients (62/66) reached SVR24 (**Figure 2**).

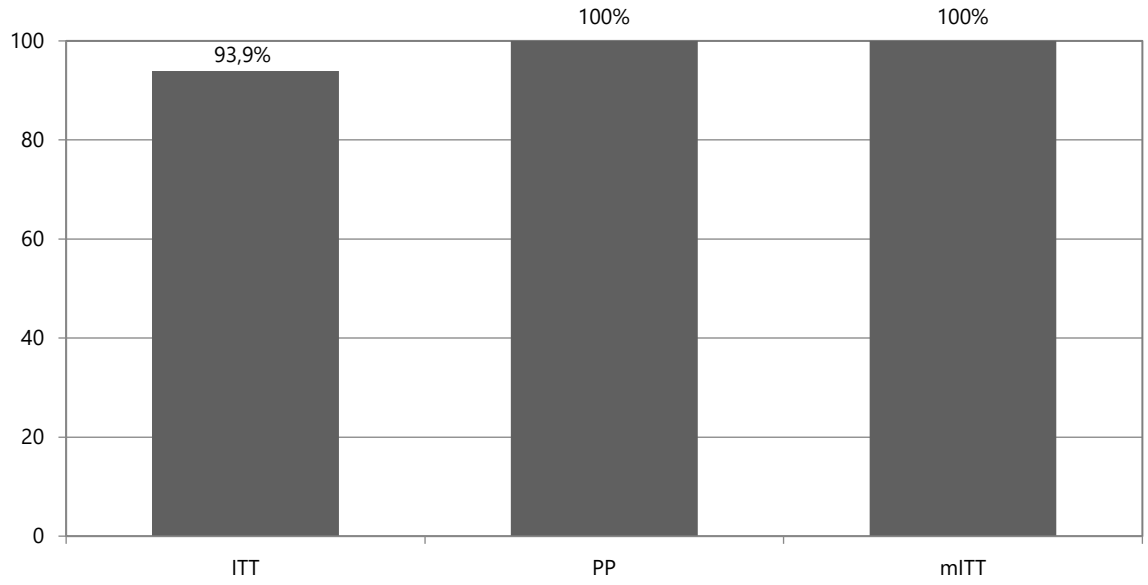

Figure 2: *3D efficacy among patients with non-compensated cirrhosis (ITT, PP and mITT amalysis). ITT (intention-to-treat), PP (per protocol), mITT (modified intention to treat). Safety of 3D regimen among patients with non-compensated cirrhosis*

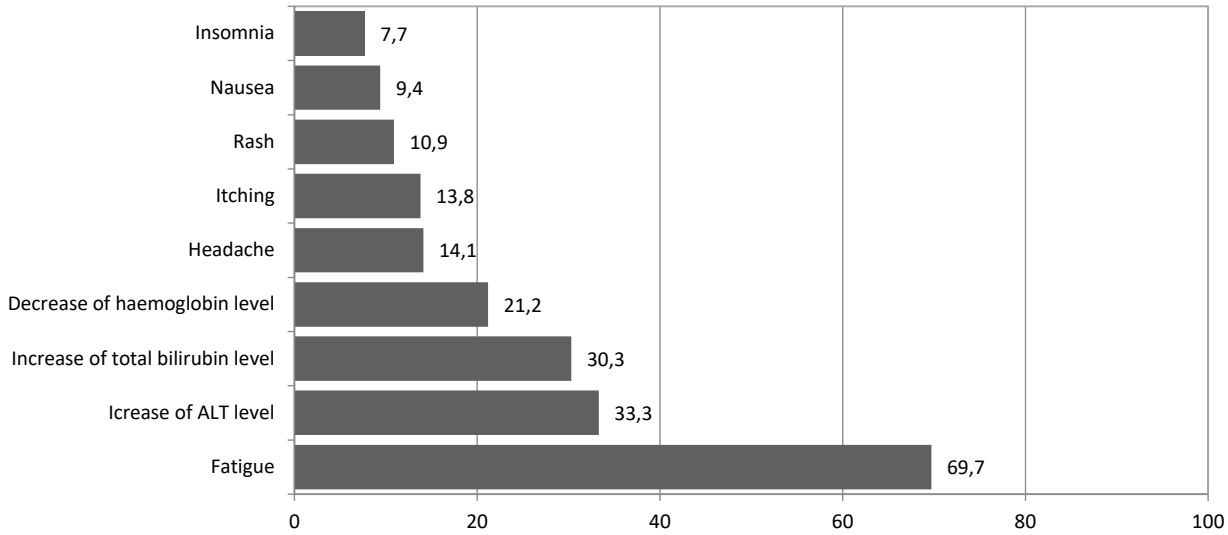

Figure 3: *Adverse events and laboratory abnormalities on 3D therapy among patients with non-compensated cirrhosis*

The following adverse events were reported during 3D therapy: nausea - 9,4%, headache - 14,1%, itching - 13,8%, rash - 10,9%. Moreover, 7,7% reported insomnia or drowsiness in day time, which could be the signs of presence or slight progression of hepatic encephalopathy. Fatigue (69,7%) was the most frequent complaint. (**Figure 3**).

14 patients (21,2%) experienced decrease in haemoglobin level not less than 10 g/dl. Anemia was associated with ribavirin usage during first 4 weeks of treatment. Its cancellation turned to rapid increase of haemoglobin and normalization of its level by the 8th week of treatment.

Change in transaminases levels among 33,3% of patients and in bilirubin level among 30,3% tasked for special attention (Figure 3). Within deeper analysis, cytolysis was limited in time to just 2 weeks among 4 patients and to 4 weeks among 18 patients, in all cases <5 x ULN. ALT increase was reported only among patients whose baseline level was higher than group average (in majority of cases not higher than 100 IU/L) (Figure 4). Thus, short time increase of ALT <5x ULN (120,9 ± 27,6 IU/L) might be considered as minor, even minimal and not associated with liver toxicity of the used regimen among the certain category of patients.

Total bilirubin demonstrated maximum growth by 57,2% up to the 4th week of therapy reaching 3,27 mg/dL in group average ($p<0,001$). After 8 weeks of therapy total bilirubin level decreased to 1,78 mg/dL, and by EOT - to 1,71 mg/dL ($p<0,001$) (Figure 5). Growth of this parameter within the first 4-8 weeks of therapy was < 3x ULN among 18 patients

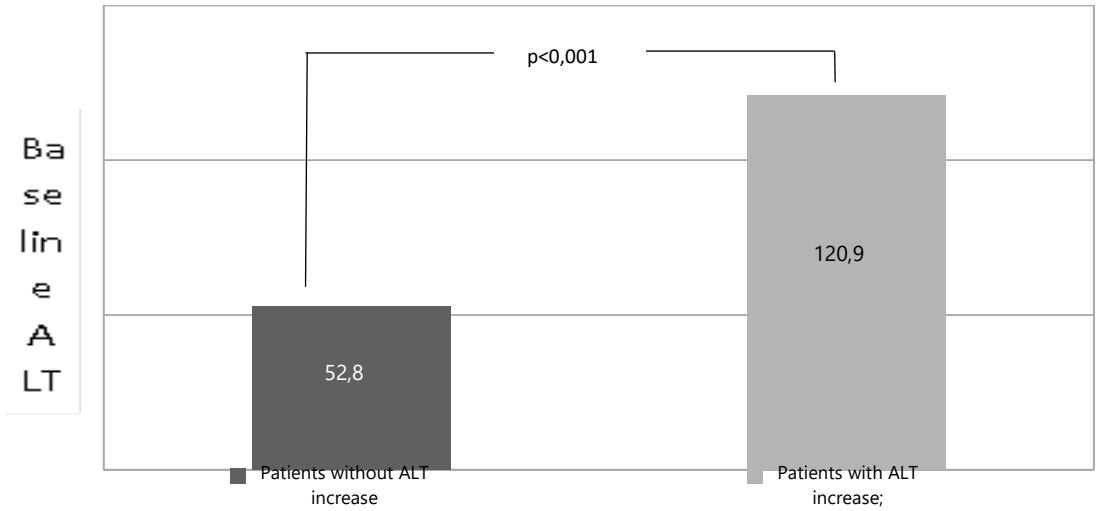

Figure 4: *Difference in baseline ALT levels among patients with and without its increase during 3D therapy*

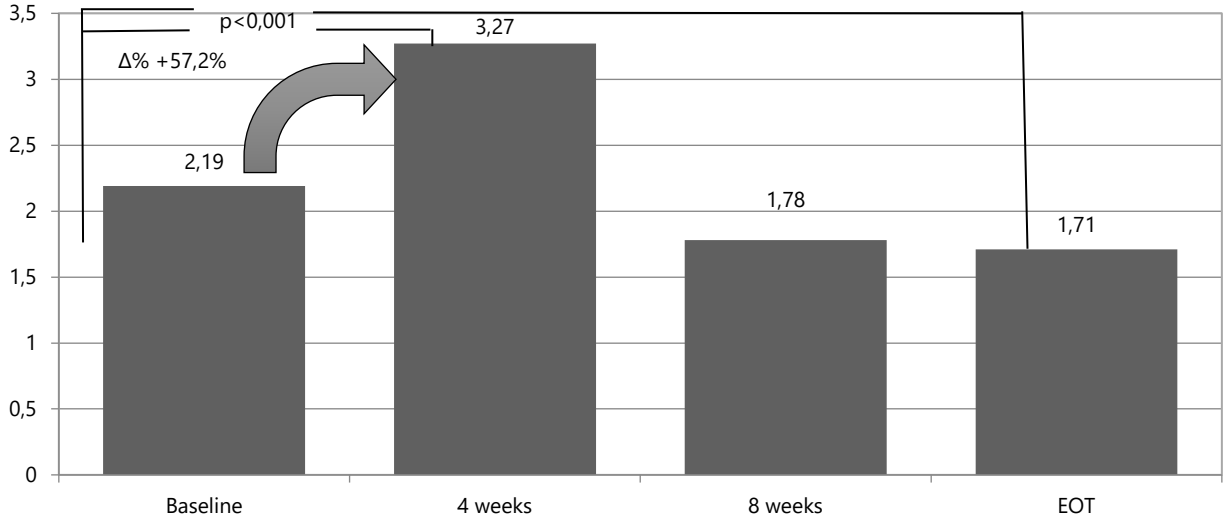

Figure 5: *Total bilirubin level dynamics during 3D therapy among patients with non-compensated cirrhosis, mg/dL*

and < 5x ULN among 17 patients. 2 patients with 10x ULN were withdrawn on days 15 and 31 of therapy. In general, increase of bilirubin level did not lead to Child-Pugh score increase.

The discussed treatment regimen demonstrated obvious positive dynamics of laboratory and instrumental parameters, characterizing level of compensation before and after reaching SVR. 21 patients (33,9%) reported decrease in Child-Pugh score by 3-4 points, 35 patients (56,5%) - by 1-2 points. 4 patients (6,5%) with stable Child-Pugh score needed longer period of recovery. The remaining 2 patients (3,2%) with the increase of Child-Pugh score were added to waiting list for liver transplantation (**Figure 6**).

Dynamics of MELD score was analyzed as well. Improvement of liver function was observed among 2/3 of patients (66,1%) who reached SVR. 12 patients (19,4%) demonstrated stable status, and 9 patients (14,5%) – negative result meaning the increase of MELD score (**Figure 7**). It grew by 4 points at SVR24 for the same 2 patients with Child-Pugh score increase.

Such factors as severity of HCV, complications of liver cirrhosis, age and co-morbidities determined certain severe adverse events, reported during 3D treatment course. 3 cases of therapy withdrawal were caused by deterioration of liver decompensation as well as 3 deaths after premature discontinuation of treatment and 1 death in follow-up period.

After 7 days of treatment jaundice (increase of total bilirubin level from 3,45 to 21,93 mg/dL) without signs of hemolysis and progression of hepatic encephalopathy occurred in 48 y.o. female patient V. with severe diabetes mellitus type II, obesity, cryoglobulinemic vasculitis, severe thrombocytopenia (platelet count 29 x103 cells/μL) and Child-Pugh score 9 points. Therapy was discontinued after 14 days which turned to involution of liver decompensation and reversion to baseline parameters.

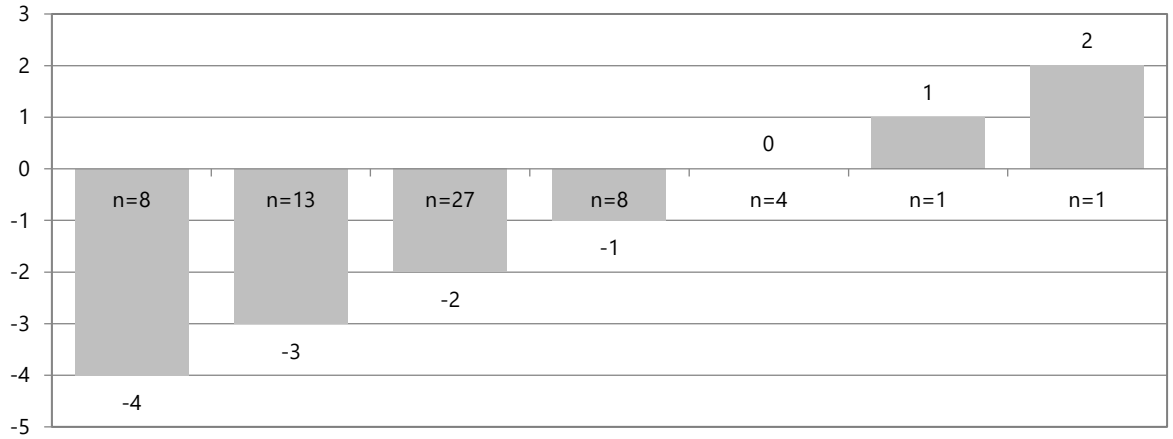

Figure 6: *Child-Pugh score dynamics: baseline and SVR24 (n=62), points*

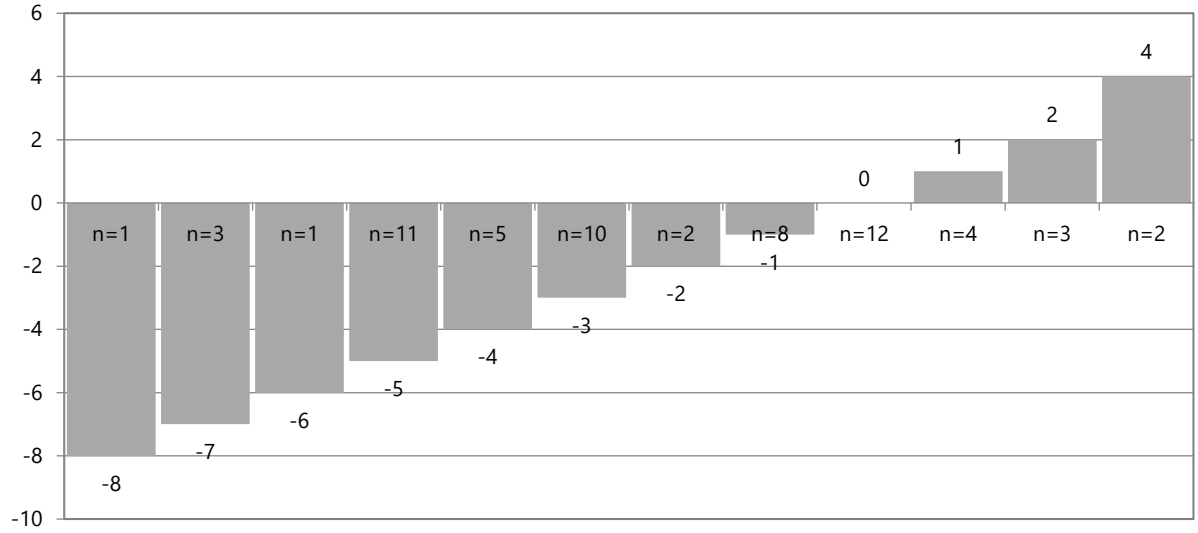

Figure 7: *MELD score dynamics: baseline and SVR24 (n=62), points*

54 y.o. male patient B. with esophageal varices ligation in anamnesis, baseline thrombocytopenia (platelet count 36 x103 cells/μL) without symptoms of bleeding, concomitant HCV-infection and alcohol cirrhosis with Child-Pugh score 9 points was urgently admitted to a hospital with invariable behavior progressed to depression of consciousness. 3D regimen was discontinued and symptoms of hepatic encephalopathy resolved within inpatient care.

Like in the 1st case, a 57 y.o. female patient M., with baseline Child-Pugh score 7 points, experienced dramatic growth of total bilirubin level from 1,57 to 18,42 mg/dL after 30 days of treatment which leaded to discontinuation of therapy. Jaundice rapidly resolved afterwards.

Progression of hepatic encephalopathy was observed in 68 y.o. female patient K., with long history of liver cirrhosis and frequent hospitalizations. Baseline Child-Pugh score was 9 points. 3D therapy was discontinued after 40 days, though no significant changes of laboratory parameters were reported. Despite of started pathogenic therapy, patient died on 23rd day after withdrawal due to hepatic coma.

Patient M., a 48 y.o. male with long time liver disease history, HCV-infection and concomitant alcohol cirrhosis with baseline Child-Pugh score 7 points, early diabetes mellitus type II was admitted to hospital after 8 weeks of antiviral therapy with pyretic fever and suspicion on pneumonia. Antiviral treatment was discontinued. Antibacterial therapy was ineffective, general status progressively deteriorated: decrease of serum albumin, anemia, respiratory insufficiency, polyserositis. After 3,5 weeks he died due to bacterial endocarditis in the setting of alcoholic dilatation without the deterioration of circulation. Alcohol use during treatment could not be excluded.

Patient P., 63 y.o. female, with mild baseline ascites and Child-Pugh score 9 points was admitted to hospital after 8,5 weeks of therapy with symptoms of gastro-intestinal bleeding which could not be stopped for 3 days and led to death. Ulcerous defects of gastric mucosa caused by portal gastropathy were found to be the sources of bleeding.

The last lethal outcome was reported for patient Z., 54 y.o. female with baseline Child-Pugh score 8 points mostly impacted by hepatic encephalopathy on 14th week of follow up due to progression of HCC. She successfully accomplished the antivital course with imperceptible growth of alpha-phetoprotein (up to 12,3 μg/L).

DISCUSSION

Interferon-free therapy became a breakthrough in overcoming existed barriers among difficult to treat HCV-infected patients. Within huge variety of clinical courses of the disease only patients with compensated cirrhosis and minimal cytopenia had a chance to be cured on the final stage of HCV-infection. Various systemic co-morbidities also applied limitations on treatment options. The 1st in Russia interferon-free regimen – "3D" became the salvage therapy for difficult-to-treat patients and afforded to broaden the spektrum of patients who can be treated. It gave an opportunity to cure even patients with non-compensated cirrhosis, especially those who had failed on previous regimens.

Generally we have received very promising treatment results among patients with non-compensated cirrhosis, even in those who withdrawn due to safety reasons on early stages of treatment (between 14 and 30 days). Achievement of SVR by our patients with no regards to symptoms of liver insufficiency, traditional negative predictors (age, metabolic status, time to reach aviremia, virologic response on previous antiviral regimen, etc.) assures us that the number of absolute contraindications to the administration of IFN-free regimens is very small.

Still during the course and after the end of treatment 3 withdrawals and 4 lethal outcomes were reported. Serious adverse events rate in our group was 10,6%. Logical question was raised, were those SAEs associated with 3D therapy and was it worth paying potential safety for the high efficacy? It is well known that presence of non-compensated cirrhosis is crucial for HCV prognosis. That is the reason why liver failure and associated risk of lethal outcome is considered to be natural for such patients. Arguing on each case of decompensation on interferon-free therapy which led to death, it is important to remember that such risk could be higher without therapy. How could HCV progress in elderly female with repeated episode of hepatic encephalopathy which led to liver coma and death without antiviral therapy? Unstable condition with Child-Pugh score 9 points could not exclude such outcome in case of no therapy. In other lethal case non-compensated cirrhosis status was aggravated by alcoholic liver disease and negative somatic status with diabetes mellitus 2nd type and alcoholic dilatational cardiomyopathy. Thus, initiated therapy probably could not be the main reason of liver failure. Absence of evident link between the therapy and lethal outcomes in rest of the patients was unarguable: undiagnosed gastro-intestinal bleeding from gastric ulcerous defects during several days in 1st case and undiagnosed HCC with normal baseline alpha-phetoprotein level in 2nd case.

Despite observed adverse events, complaints and laboratory abnormalities, OBV / PTV / r ± DSV ± RBV therapy for patients with non-compensated cirrhosis was generally well tolerated. We may assume that negative impact on development of adverse events could be driven by ribavirin within first 4 weeks of regimen. 90,9% patients in non-compensated cirrhosis cohort reported adverse events. This number is very much in line with the results of registration studies for HCV Gt 1 patients where overall safety issues were reported in 67%-92% patients with fibrosis F0-F3 (23, 24) and in 90,7% -91,8% (25) patients with compensated cirrhosis.

Despite of no direct indications of 3D-therapy for patients with non-compensated liver function (Child-Pugh B), post marketing reports on aggravation of liver decompensation did not confirm the linkage between certain regimen and progression of liver insufficiency (26).

From the other hand we may conclude that despite common recommendation to avoid using 3D therapy on non-compensated cirrhosis stage, our experience allowed 62 patients to get cured from HCV. It means that all of them received an opportunity to slow down cirrhotic progression which has been proven by the decrease in Child-Pugh and MELD scores in 6 months after EOT.

Thus, clear understanding of negative perspectives of disease progression makes it reasonable to use the unique chance to save patients' lives. Only in such cases the risk may be justified.

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