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USAGE OF NUKLEX IN THERAPY OF PATIENTS WITH HEPATITIS C

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Usage of Nuklex for treatment of hepatitis C is accompanied by a rapid disappearance of the main clinical symptoms, improvement of health in the patients, supports normalization of cytolytic liver function in patients with minimal or moderate activity hepatitis. Based on the obtained data, it can be considered the isolate usage of Nuklex as the only antiviral drug for hepatitis C patients with low initial viral load HCV (<800,000 IU/ml) in a daily dose of 1.5 g. It is rather prospective to continue to study the efficiency of Nuklex in patients with hepatitis C with an initial high viral load HCV (>800,000 IU/ml) in complex therapy with other antiviral drugs.

Key words *hepatitis C, cytolysis, viral load.*

3 % of the population of the planet suffers from virus hepatitis C (HC), and every year this pathogen infected up to 3-4 million people [1, 2]. Ukraine belongs to regions with high population infected by virus HC, where only in-patient monitoring is more than 280 thousand patients of different etiology. The effectiveness of existing therapies, so called “gold standard”, based on Peginterferon combined with Ribavirin in a considerable number of patients is unsatisfactory. Thus, the effectiveness of treatment in patients with HC genotypes 2 and 3 is about 80 %, while for other genotypes does not exceed 40-50 % [3]. This therapy is accompanied by the development of adverse effects in 20 % of patients who prematurely forced her to stop, and in some patients, there are contraindications for the specific therapy. So far the search for new treatments of patients with HC is still in process. The most promising direction is the use of specific drugs that affect the replication of the virus.

Among the latest trends, HC treatment search find drugs can modulate inflammatory responses and antiviral innate immunity to fight viral infections. Previously, we developed and patented by the U.S., EU, China, India, Ukraine and Eurasia technology selection of homogeneous fractions of yeast micro RNAs, which, together with antiviral activity, has anti-inflammatory and immunomodulatory activity [4, 5, 6]. Based on the substance of this company “DP Biosel” developed and registered in Ukraine Nuklex drug with a specific antiviral effect [7].

Preparations based on yeast RNA has long used in clinical practice as immunomodulators in treatment of infectious diseases [8]. The first work on the clinical use of drugs in the treatment of yeast RNA chronic hepatitis were made in the Voronezh Medical Institute led by professor Zemskova. It was shown that the use of sodium Nukleinats as immunomodulators in the treatment of chronic hepatitis B leads to complete correction of secondary immunodeficiency and significantly improve the clinical condition of the patient [9]. However, preparations yeast RNA sodium salt characterize by great heterogeneity on molecular weight, whether proteins, polysaccharides and a large number of DNA [5]. Studies have shown that the composition includes sodium Nukleinats macromolecular transport and RNA low-molecular mono-and oligonucleotides [10]. This heterogeneous, crude drug has only immunomodulating activity and showed anti-inflammatory action.

At the same time, as shown by prolonged study of this pathology at the forefront symptoms of exacerbations is an inflammatory process of chronic hepatitis [11]. Therefore, once company ‘DP Biosel’ registered and introduced to market a new immunomodulator with anti-inflammatory activity of Nukleinat, he immediately drew the attention of clinicians and was used for the treatment of chronic hepatitis [12].

Substance from which produced Nuklex consists of especially pure, homogeneous 25-parts oligorybonukleotidis clean DNA, proteins and polysaccharides. As a result of temperature changes the conformation processing of oligorybonukleotidis molecules takes place, which leads to the acquisition of specific antiviral activity, stably stored for a long time [4]. Nuklex possesses membrane, anti-inflammatory action [13], stimulates the processes of

cellular metabolism, increases endogenous biosynthesis of nucleic acids, specific proteins and enzymes [7], enhances mitotic activity of bone marrow cells [14] in experimental models and in clinical practice shows a broad antiviral effect including against hepatitis C virus, even when isolated its use in patients with a low number of virus [15-18].

Its objective was to study the effectiveness of the drug Nuklex in the treatment of patients with HS and the optimal therapeutic dose.

Patients and methods

Under observation were 12 patients with hepatitis C (HC) in the phase of virus replication, aged 18 to 47 years (average age 36,8 ± 9,37 years), equal to 6 men and women. Most patients are urban residents (10 persons, 83.3 %). From the epidemiological history, attention is drawn blood transfusion – 4 patients (50 %), surgery – 3 (25 %), donation – 2 patients (16.68 %), all patients confirmed visiting the dentist. Absence of specific clinical symptoms do not allow clearly establish the duration of illness, but in 8 patients (66.67 %) term diagnosis of HS does not exceed three months.

The diagnosis of HS was established by ELISA blood test for the presence of markers of hepatitis C virus (HCV) and confirmed by polymerase chain reaction (PCR RNA HCV). In conducting genotyping of HCV was found that the major genotype of hepatitis C virus was the first b (1b), which is found in 6 people (50 %), genotype 3 in one patient (8.33 %) patients in other genotype of the virus is not determined. Prevail in patients with high viral load (>800,000 IU / ml) RNA copies NSV (8 patients, 66.7 %).

During the study, patients received no other specific antiviral treatment. Two (16.66 %) of patients in the past received antiviral therapy at the GS, and there was not obtained positive results (non-responders).

Among patients with HC were dominated by patients with moderate activity (8 persons, 66.7 %) and in 4 patients (43.3 %) identified the minimum active hepatitis. Among the studied patients with HC in both groups were found highly active hepatitis.

Depending on the treatment received, patients were divided into two groups. Patients and groups (5 persons) received treatment under the scheme 1st month – Nukleks to 1K 3 times a day, Rybaryn considering the patient's weight 5 times a day, second month – on Nuklex 1K 2 times since the third month – Nuklex to 1K 1 time a day. Patients II group (7 persons) Nuklex dose was increased twice, so they got Nuklex in 2 to three times a day, and in the first month of treatment additionally Rybaryn. In groups, patients were divided according to the criteria of hepatitis activity (indicators of cytolysis) – Group "A" – minimum activity (IA and IIA in 2 patients), "B" – moderate activity (IP – 3 patients and IIV – 5 patients) and performance viral load: group "a" – low level (Ia and IIa in 2 patients) and "B" – high viral load (John – 3 and Yves – 5 patients). Duration of treatment was six months.

To address this goal were used the following methods: general clinical examination, biochemical, virological methods (PCR RNA HCV, amount of virus in the blood), instrumental methods (ultrasound organs of abdominal cavity). Particular attention is paid to indicators of cytolysis, which characterizes the activity of hepatitis (ALT level) and viral load. There were studied parameters in the dynamics.

Statistical analysis of conducted survey results was done with statistical methods in clinical trials [19].

By the beginning of the study patients of both groups filed similar complaints of pain in right hypochondrium, joints, loss of appetite, sleep disturbance, general weakness (Table 1).

Table 1

Characteristic complaints of patients with HC in the studied groups

№	Complaints	Number of patients with HC			
		I group (n=5)		II group (n=7)	
		Abs.	%	Abs.	%
1	Headache	3	60	4	57.14
2	Pain in the right under the ribs	5	100	6	89.4
3	Decrease of appetite	5	100	6	89,4
4	Weakness	5	100	7	100
5	Sleep disorders	3	60	5	71.45
6	Nausea	3	60	5	71.45
7	Dry mucous membranes	3	60	5	71.45
8	Pain in the joints	4	80	6	89.4
9	Allergic manifestations	2	40	4	57.14
10	Haemorrhage	1	20	1	14.29
11	Weight loss	3	60	4	57.14

As illustrated by Table 1, significant difference claims in groups of patients with HC haven't been identified.

Duration of complaints in groups of patients under the influence of treatment also did not differ significantly in the studied groups. In all HC patients diagnosed liver enlargement, increasing of its echogenicity (according to ultrasound examination of organs of abdominal cavity). In two patients (16.66%) on the skin were found manifestations of hemorrhagic syndrome in the form of petechiae in the injection. Manifestations and duration of objective symptoms in patients of both groups also did not differ significantly. It should be noted that among our patients were patients with signs of cirrhosis. During treatment there were not marked increase of symptoms, adverse events, disease progression. Patients of both groups are well tolerated drug, regardless of the Nuklex dose (Table 2).

Table 2

Duration of complaints in patients with HC in the studied groups

№	Complaints	Duration of complaints, days	
		I group (n=5)	II group (n=7)
1	Headache	6.04±0.32	5.22±0.27
2	Pain in the right under the ribs	9.86±0.69	8.76±0.23
3	Decrease of appetite	8.32±0.34	8.33±0.28
4	Weakness	10.45±0.51	9.68±0.48
5	Sleep disorders	7.33±0.87	8.06±0.97
6	Nausea	3.25±0.86	4.01±0.97
7	Dry mucous membranes	5.06±1.02	4.97±0.68
8	Pain in the joints	9.54±0.67	8.98±1.03
9	Allergic manifestations	3.06±0.5	2.8±0.5
10	Haemorrhage	2	2
11	Weight loss	15.9±1.98	16.7±0.89

Describing the dynamics of laboratory parameters in patients with HC we should pay attention primarily on biochemical parameters that characterize the activity of hepatitis. Dynamics of the main biochemical parameters under the influence of treatment is reflected in Table 3.

Table 3

Dynamics of biochemical parameters in patients with HC under the influence of treatment

№	Indicators and their normal magnitude	Groups of patients			
		I group (n=5)		II group (n=7)	
		Before treatment	After treatment	Before treatment	After treatment
1	Bilirubin common, (1.7–20.5mmol/l)	24.05±0.98	18.9±0.51	21.91±1.34	17.6±0.48
2	Bilirubin direct, (0-5 mmol/l)	5.41±0.87	2.86±0.29	10.98±0.48	3.59±0.87
3	ALT, (0.1–0.45 mmol/p•l)	1.48±1.64	0.5±0.76*	1.512±0.65	0.32±0.42*
4	AST, (0.1–0.68 mmol/p•l)	1.35±1.32	0.37±0.23	1.29±0.37	0.37±0.57
5	Protein common, (65–85 g/l)	71.5±0.59	69.1±0.47	74.0±0.81	72.96±0.34
3	Albumins, (55 – 65 %)	60.5±0.83	55.42±0.68	52.7±0.92	59.62±0.38
7	Globulins, (45–35 %)	39.5±0.76	44.58±0.82	47.3±0.3	40.38±1.24

Note: * – differences in accuracy compared to pre-treatment, $P < 0.05$

According to the table, under the influence of Nuklex was marked improvement of biochemical parameters in patients with HC, regardless of dose. A small number of patients do not allow demonstrating the accuracy of positive dynamics in the reduction of activity of hepatitis. The analysis of cytolysis in patients with HC with different degrees of activity under the influence of Nuklex demonstrates clearly the dynamic effect on performance cytolysis especially in patients with moderate activity of HC (diagram 1).

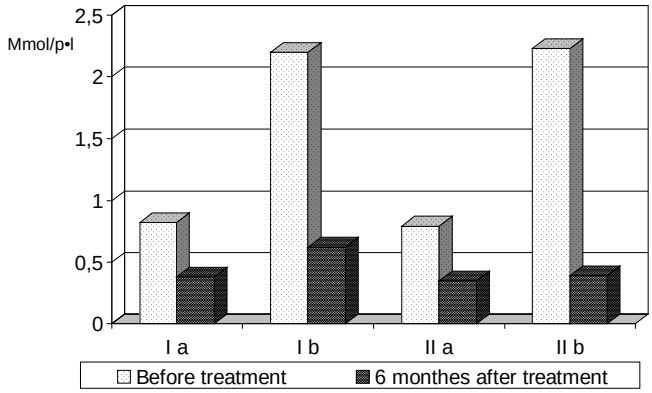

Diagram 1. Dynamics of ALT in patients with HC under the influence of treatment.

Dynamics of cytolysis in patients with HC with moderate activity more pronounced in patients taking Nuklex at a dose of 1.5 g per day (IIb group), indicating a lack of toxic effects of the drug and of higher anti-inflammatory effect of Nuklex with this dosage. It should be noted that normalization of biochemical parameters in patients with HC with moderate activity was advancing from the second week of treatment and remained stable for six months.

Dynamics of viral load averages under the influence of treatment of Nuklex also not reliably reflect the effect of the drug on the virus of hepatitis C. However, the antiviral effect of using Nuklex depending on the initial viral load in patients with HC is clearly depicted in diagram 2.

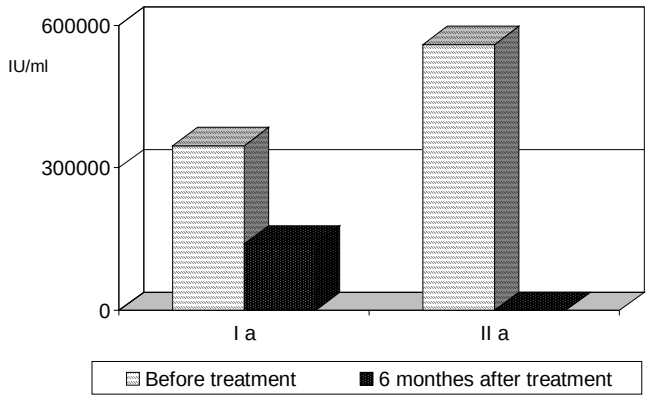

Diagram 2. Dynamics of viral load in patients with HC under the influence of treatment.

According to diagram 2 in patients with low initial viral load after six months of Nuklex use in a daily dose of 0.75 g per day (group Ia) observed significant reduction in the concentration of virus in the blood. When applying of Nuklex dose 1.5 g per day (group IIa) from three months after starting treatment of HC virus is not determined in the blood.

Dynamics of viral load in patients with HC with a high initial level of virus concentration (group I c and IIc) under the influence of treatment demonstrating lack of effect using only Nuklex for such patients. It was received an early positive response when used together with Nuklex and Rybaryn in the first month of treatment, even in patients – non-responders (average concentration of HCV RNA decreased from 9.59×10^6 to 1.06×10^5 IU/ml). However, further isolation of Nuklex use in patients of these groups was accompanied by fluctuations in the concentration of the virus and not led to its fair decrease (final concentration RNA HCV 1.029×10^6 IU/ml).

Thus, the dynamics of biochemical parameters and viral load can be used to offer Nuklex isolation for treatment of HC with low viral load in a dose of 1.5 g per day. Obtained in the course of the study results are not convincing enough to recommend the use of Nuklex as the only antiviral drug in patients with HC with a high concentration of virus in the blood. However, there is a need in an additional study in use of Nuklex in the treatment with other antiviral drugs, due to its pronounced anti-inflammatory and immunomodulatory effects.

Conclusions

1. Usage of Nuklex for treatment of hepatitis C is accompanied by a rapid disappearance of the main clinical symptoms, improvement of health in the patients, supports normalization of cytolytic liver function in patients with minimal or moderate activity hepatitis.

2. Based on the obtained data, it can be considered the isolate usage of Nuklex as the only antiviral drug for hepatitis C patients with low initial viral load HCV (<800,000 IU/ml) in a daily dose of 1.5 g.

3. It is rather prospective to continue to study the efficiency of Nuklex in patients with hepatitis C with an initial high viral load HCV (>800,000 IU/ml) in complex therapy with other antiviral drugs.

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ЗАСТОСУВАННЯ НУКЛЕКСУ В ТЕРАПІЇ ХВОРИХ НА ГЕПАТИТ С

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РЕЗЮМЕ. Встановлено, що використання нуклексу для лікування хворих на гепатит С супроводжується швидким зникненням основних клінічних симптомів, поліпшенням стану здоров'я, підтримує нормалізацію цитолітичної функції печінки, передусім у пацієнтів з мінімальною або помірною активністю гепатиту. На підставі отриманих даних можна вважати доцільним використання нуклексу у хворих з низьким початковим рівнем навантаження HCV (<800 000 МО/мл) у добовій дозі 1,5 г. Досить перспективним видається продовження вивчення ефективності нуклексу в пацієнтів з гепатитом С з початковим високим навантаженням HCV (>800 000 МО/мл) у комплексній терапії з іншими противірусними препаратами.

Ключові слова: *гепатит С, цитоліз, вірусне навантаження.*

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