CLINICAL

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THE COMBINED TREATMENT OF CHRONIC VIRAL HEPATITIS B, C AND MIXED B AND C WITH CITOMIX™+GUNA®-LIVER+ INTERFERON GAMMA 4C

SUMMARY

Seventeen patients have been included in this clinical study (9 men and 8 women, aged between 18 - 80): 8 of them were diagnosed with chronic viral hepatitis B (HVBC), 7 with chronic viral hepatitis C (HVCC) and 2 patients with mixed chronic viral hepatitis B+C (HVBC+HVCC) - the experimental Group.
The control Group is made up of 16 patients (10 men and 6 women, aged between 27 and 72): 6 diagnosed with HVBC, 8 with HVCC and 2 patients with mixed chronic viral hepatitis B+C.
The diagnosis has been confirmed by specific laboratory tests (AgHBs, AgHBe anti-HBe, anti-HBc HVBC anti-HVC, anti-HVC IgM HVCC).
The combined treatment was indicated for a period of three months:
- Citomix™: 10 pellets, twice a day (morning and evening) for the first 5 days; afterwards 3 pellets twice a day for 6 consecutive days week.
- Guna®-Liver: administered after 15 minutes, 3 pellets twice a day (morning and evening) per 3 months.
- Interferon γ 4C: 20 drops twice a day (in the morning and evening) for 3 months.
Medicines were recommended to be administered one hour before or after meals.
Patients have been monitored at the beginning of the therapy and after one, two months and at the end of it through clinical and laboratory tests: bilirubin, ALAT, ASAT, thymol test, prothrombin index and serologic tests (in HVBC patients - determination of AgHBe, anti-HBe and anti-HBs at the treatment start and end; in HVCC- the determination of anti-HCV IgM at the treatment start and end) and hemogram; immune status at the start and end of treatment.
The combined treatment with Citomix™ + Guna®-Liver + Interferon γ 4C has proved to be more effective: clinical symptoms improvement in patients with HVBC, HVCC and HVBC+HVCC; decrease and normalization of liver and spleen sizes; moderate decrease of liver cytolisis indices values (ALAT, ASAT); seroconversion AgHBs and anti-Hbs with formation of anti-HBs (protective antibodies) in 2 patients with HVBC and in one patient with the mixed hepatitis HVBC+HVCC; immune status improvement, which was more marked in patients with HVCC.
It has not been demostrated any clinical, biochemical and immunological improvement in patients of the control Group.

KEY WORDS **HVBC, HVCC, CITOMIX™, GUNA®-LIVER, INTERFERON γ 4C**

INTRODUCTION

1. The viral hepatitis problem remains to be one of worldwide significance, with its consequences affecting the health of hundreds of million of people. Fundamental types of the disease include viral, acute and chronic hepatitis. New therapeutical methods have appeared recently in medical practice, beginning with the antiviral drugs which have counterindications and side effects. Only 30–40% of patients usually benefit from antiviral treatment, but what about the rest?
2. The purpose of the study was to determine the efficacy of Citomix™ + Guna®-Liver + Interferon gamma 4C in viral chronic hepatitis B, C and B +C

PATIENTS AND METHODS

2 patient groups were included in the study:
- First group - the patients were administered three therapies: **Citomix™ + Guna®-Liver + Interferon γ 4 C: 17 patients = experimental group**.
- Second group (control group):**16 patients = control group**.

Seventeen patients were included **in the experimental group**: 9 men and 8 women aged between 18 and 80 years, among them 8 were diagnosed with HVBC, and the disease stage was between 1 and 13 years; 7 patients were diagnosed with HVCC, and the disease stage was between 1 and 9 years and 2 patients were diagnosed with mixed chronic viral hepatitis B+C, in one patient the disease stage was equal to 1 year, and in the second HVBC was detected 28 years before, and HVCC was revealed 2 years ago.
- There were 16 patients included in **the control group**: 10 men and 6 women aged between 27 and 72 years.
Among them 6 patients with the diagnosis of HVBC, 8 patients with the diagnosis of HVCC, and 2 patients with mixed chronic viral hepatitis B+C.
The disease length was between 5 to 17 years in patients with HVBC. The disease length was between 1 to 12 years in patients with HVCC. The disease length in patients with mixed chronic viral hepatitis B+C was as follows: in one patient both hepatitis forms were traced 8 years before and in the second patient HVCC was diagnosed 12 years ago, and HVBC – 10 years ago.

The clinical exams

Patients with HVBC, HVCC and mixed HVBC+HVCC were clinically examined: anamnesis, liver and spleen palpation and percussion, chest auscultation and percussion and heart auscultation.

The dynamics of paraclinical and clinical investigations:

- **Laboratory exams**: serologic investigations revealing AgHBe, anti-HBe, anti-HBs, anti-HVC IgM; biochemistry investigations: values of ALAT, ASAT, bilirubin, thymol test, prothrombin; **clinical exams**: hemogram and immunological status were made at the start and at the end of treatment.

The treatment lasted for 3 months.

The method of medicine administration in the First group was as follows:

The first month of treatment

1• Interferon gamma 4C: 26 days, 20 drops twice a day sublingually (in the morning and evening), one hour before meals or one hour after meals.

On Sundays the medicine was not administered.

2• Guna®-Liver: 26 days, 3 pellets twice a day sublingually in the morning and evening, one hour before meals or one hour after meals.

The medicine was indicated to be administered 15 minutes after the administration of Interferon gamma 4C.

3• Citomix™: 10 pellets twice a day sublingually, in the morning and evening for the first 5 days, and for the next 21 days 3 pellets twice a day sublingually in the morning and evening, 15 minutes after the administration of Guna®-Liver. On Sundays the medicine was not administered.

The second and the third month of treatment

1• Citomix™: 26 days, 3 pellets twice a day sublingually in the morning and evening, one hour before meals or one hour after meals.

2• Guna®-Liver: 26 days, 3 pellets twice a day sublingually in the morning and evening, 15 minutes after Citomix™ administration.

3• Interferon gamma 4C: 26 days, 20 drops twice a day sublingually in the morning and evening, 15 minutes after Guna®-Liver administration.

SYMPTOM	AT THE TREATMENT'S START			AT THE TREATMENT'S END		
	HVBC n=8	HVCC n=7	HVBC+HVCC n=2	HVBC n=8	HVCC n=7	HVBC+HVCC n=2
Asthenia	3 (37,5%)	-	1	1 (12,5%)	-	-
Pain in the right hypochondrium	5 (62,5%)	2 (28,5%)	-	1 (12,5%)	-	-
Vertigo	2 (25%)	-	-	-	-	-
Myalgia	1 (12,5%)	2 (28,5%)	1	-	-	-
Joints pain	1 (12,5%)	2 (28,5%)	-	-	-	-
Nausea	2 (25%)	-	1	-	-	-
General weakness	2 (25%)	-	-	-	-	-
Pruritus	1 (12,5%)	-	-	-	-	-
Hepatomegaly	6 (75%)	5 (71,7%)	2	2 (25%)	3 (43%)	1
Splenomegaly	5 (62,5%)	3 (43%)	1	1 (12,5%)	1 (14,3%)	1

TAB. 1

Clinical symptomatology and its evolution dynamics in patients of the experimental group.

SYMPTOM	AT THE TREATMENT'S START			AT THE TREATMENT'S END		
	HVBC n=6	HVCC n=8	HVBC+HVCC n=2	HVBC n=6	HVCC n=8	HVBC+HVCC n=2
Asthenia	5 (83%)	2 (25%)	-	4 (66,6%)	1(12,5%)	-
Pain in the right hypochondrium	3 (50%)	5 (62%)	1	3 (50%)	2 (25%)	-
Vertigo	-	1 (12,5%)	-	-	1 (12,5%)	-
Myalgia	1 (16,6%)	-	-	-	-	-
Joints pain	1 (16,6%)	2 (25%)	-	-	2 (25%)	-
Nausea	1 (16,6%)	1 (12,5%)	-	1 (16,6%)	1 (12,5%)	-
General weakness	3 (50%)	2 (25%)	-	3 (50%)	1 (12,5%)	-
Prurigo	-	-	-	-	-	-
Hepatomegaly	5 (83%)	7 (87,5%)	1	5 (83%)	7 (87,5%)	1
Splenomegaly	5 (83%)	4 (50%)	2	5 (83%)	4 (50%)	2

TAB. 2

Clinical symptomatology and its evolution dynamics in patients of the control group.

TAB. 1 demonstrating mild symptomatology, but the following symptoms were observed with a higher frequency: pain in the right hypochondrium, asthenia, hepatomegaly, and splenomegaly.

The clinical symptomatology was richer at the treatment start in patients with HVBC. They demonstrated a wider range of symptoms compared to patients with HVCC and HVBC+HVCC.

The **clinical symptomatology ameliorated after 3 months of treatment**, and at the end of it, only 2 clinical symptoms persisted: asthenia and pain in right hypochondrium in patients with HVBC. The liver and spleen dimensions had

decreased in all three groups with a decrease of **over 50%** at the treatment's end compared to the liver and spleen dimensions at the treatment's start.
The clinical symptomatology in patients of the control group is shown in TAB. 2 demonstrating the low frequency of clinical manifestations, and being largely the same both in patients with HVBC and HVCC. The analysis of the evolution of these symptoms in dynamics revealed insignificant amelioration.
Hepatomegaly and splenomegaly were revealed with the same frequency: 83% and 87.5% respectively at the start and the end of the study.
The analysis of biochemical indices in patients of the experimental group leads us to some conclusions (TAB. 3):
- ALAT had normalized in a small number of patients - 2 with HVBC and 4 with HVCC, and the increased ASAT values had normalized in 4 patients, and had increased discreetly in 4 patients with normal values.
- Increased bilirubin values had been revealed in patients with the Gilbert's Syndrome - 30 mcmol/l and 24 mcmol/l.
- Thymol test values did not change.
- The prothrombin index was normal in the majority of patients included in the study and only in one patient with the diagnosis of HVBC and 2 with HVCC it had decreased by 70 – 80%.
TAB. 4 reveals the absence of modification in biochemical indices during three months of observation in the control group.

TAB. 5 shows the AgHBe revealed at the start and the end of treatment in the same patients; seroconversion of HBe-anti-HBe had not occured.
AntiHBs had formed in 2 patients with the diagnosis of chronic viral hepatitis B and in one patient with mixed chronic viral hepatitis B+C. This fact demonstrated a beneficial action of the three therapies with Interferon gamma 4C+Guna®-Liver+Citomix™.
These medicines probably possess antiviral actions.
IgM Anti-HVC was revealed with the same frequency at the start and the end of treatment. This fact demonstrates the absence of antiviral properties of the hepatitis C virus.
Data from TAB. 6 demonstrate the absence of AgHBe in patients of the control group. TAB. 7 shows an immuno suppression of T cells in HVBC patients at the treatment's start: 3rd degree -37,5%, 2nd degree -50%, with augmentation of B lymphocytosis in 75% the cases.

BIOCHEMICAL INDICES	AT THE TREATMENT'S START			AT THE TREATMENT'S END		
	HVBC n=8	HVCC n=7	HVBC+HVCC n=2	HVBC n=7	HVCC n=5	HVBC+HVCC n=2
ALAT (increased)	7	6	2	5	2	1
ASAT (increased)	5	4	1	5	4	1
Bilirubin (increased)	1 (Gilbert's Syndrome)	2 (Gilbert's Syndrome)	-	2 (Gilbert's Syndrome)	1 (Gilbert's Syndrome)	-
Thymol test (increased)	4	5	1	4	5	1
Prothrombin Index (decreased to 70%)	1	2	1	1	1	1

TAB. 3

The dynamics of biochemical indices in patients of the experimental group at the start and end of treatment.

BIOCHEMICAL INDICES	AT THE TREATMENT'S START			AT THE TREATMENT'S END		
	HVBC n=6	HVCC n=8	HVBC+HVCC n=2	HVBC n=6	HVCC n=8	HVBC+HVCC n=2
ALAT (increased)	4	5	1	4	4	1
ASAT (increased)	4	4	-	4	5	1
Bilirubin (increased)	3	1	-	3	-	-
Thymol test (increased)	3	1	2	1	2	-
Prothrombin Index (decreased to 70%)	2	3	2	2	2	-

TAB. 4

The dynamics of biochemical indices in patients of the control group.

MARKERS	AT THE TREATMENT'S START			AT THE TREATMENT'S END		
	HVBC n=8	HVCC n=7	HVBC+HVCC n=2	HVBC n=8	HVCC n=7	HVBC+HVCC n=2
AgHBe	1	-	-	1	-	-
Anti-HBe	7	-	2	7	-	2
Anti-HBs	-	-	-	2	-	1
Anti-HVC IgM	-	7	2	-	7	2

TAB. 5

The dynamics of markers (serologic indices) in patients of the experimental group.

An emprovement of T cells up to the normalization of the values at the treatment's end was recorded in **37,5%** of the patients.
There was a determined immunosupression: 3rd degree - in 14.3%, 2nd degree - in 71.4% and a B lymphocytosis 2nd degree – in 57.1%, an increased level of CIC – in 28.5% of patients with HVCC.
An improvement of immunosupression until normal values was reached in 42.8%, with the normalization of B lymphocytosis in 57.1% of patients at the end of treatment, but in **42.8%** there was an observed tendency toward a B lymphocytosis increase in the 1st degree as a result of the humoral reactivity.
CIC returned to normal limits in 85.7% and only in one single patient it persisted at increased values, but there was a considerable decrease – approximately twice (14,3%).

There were no positive modifications found in patients diagnosed with mixed chronic hepatitis B+C after treatment. This fact was probably is due to the small number of patients included.
TAB. 8 shows a persistence of T cell immunosuppression in the 2nd and 3rd degree in all patients from the control group, constituting 81.3% and B lymphocytosis in the 2nd degree in 68.7%; high level of CIC in 18.75% at the start of treatment and with a tendency for increase in 43,7% during the study.
These data confirm the need for a treatment of immunomodulation.

MARKERS	AT THE OBSERVATIONS' START			AT THE OBSERVATIONS' END		
	HVBC n=6	HVCC n=8	HVBC+HVCC n=2	HVBC n=6	HVCC n=8	HVBC+HVCC n=2
AgHBe	-	-	-	-	-	-
Anti-HBe	6	-	1	6	-	1
Anti-HBs	0	-	-	0	-	0
Anti-HVC IgM	-	6	1	-	6	1

TAB. 6

The dynamics viral markers in patients of the control group.

INDICES	NORMAL VALUES	AT THE TREATMENT'S START			AT THE TREATMENT'S END		
		HVBC n=8	HVCC n=7	HVBC+HVCC n=2	HVBC n=8	HVCC n=7	HVBC+HVCC n=2
Leukocytes (10^9/l)	4,5-8,0	7,625±0,851	5,828±0,459	5,05±0,45	7,162±1,08	6,614±0,914	5,0±0,6
Lymphocytes (%)	22-38	31,625±2,499	32,142±3,261	40±4	35,125±3,286	33,428±3,379	35,5±0,5
Lymphocytes (10^9/l)	1,2-2,4	2,395±0,309	1,775±0,182	2,06±0,36	2,393±0,277	2,085±0,219	1,8±0,3
Lymphocytes Ta (%)	20-34	21,5±2,352	19±3,199	19,5±8,5	19,375±2,583	18,428±1,95	20,5±3,5
Lymphocytes Ta (10^9/l)	0,3-0,7	0,517±0,103	0,364±0,072	0,45±0,25	0,505±0,108	0,402±0,062	0,4±0,1
Lymphocytes Ttot (%)	55-75	45,625±3,035	40,857±2,364	40,5±1,5	45±4,246	45,285±4,892	53,5±19,5
Lymphocytes Ttot (10^9/l)	0,9-1,5	1,072±0,197	0,755±0,112	0,86±0,16	1,178±0,222	0,985±0,166	0,91±0,19
Lymphocytes Tterm (%)	0-5	4,75±2,335	4,571±1,862	6±4	0	0	0
Lymphocytes Tterm (10^9/l)	0-0,09	0,126±0,072	0,085	0,135±0,105	0	0	0
Lymphocytes TFR-E-RFC (%)	38-58	28,875±2,286	26,428±2,457	25±2	28,625±2,764	31,428±3,329	37,5±11,5
Lymphocytes TFR-E-RFC (10^9/l)	0,7-1,1	0,71±0,128	0,491±0,096	0,52±0,13	0,756±0,114	0,677±0,122	0,67±0,07
Lymphocytes TFS (%)	12-28	16,75±1,997	14,428±1,659	15,5±0,5	16,875±2,191	13,428±2,021	16±8
Lymphocytes TFS (10^9/l)	0,23-0,43	0,406±0,077	0,252±0,032	0,315±0,045	0,448±0,103	0,275±0,041	0,265±0,095
Lymphocytes EAC-RFC (%)	9-18	31±3,835	26,428±2,715	25,5±1,5	33,75±4,934	25,285±3,727	35,5±4,5
Lymphocytes EAC-RFC (10^9/l)	0,18-0,32	0,753±0,156	0,481±0,085	0,525±0,125	0,873±0,178	0,482±0,053	0,655±0,185
CIC (U.E.)	≤ 60	42,625±8,635	72±29,125	67±22	41±9,924	51,166±34,82	133,5±26,5
LTL	4-7	7,78±0,718	8,422±1,080	5,95±0,55	6,756±0,753	7,171±0,722	5,85±1,85
T/B	2,0-5,0	1,632±0,204	1,628±0,124	1,6	1,512±0,182	2,028±0,395	1,625±0,775
TFR/TFS	2,0-4,0	1,992±0,370	2,0±0,303	1,6±0,2	1,862±0,265	2,442±0,218	2,675±0,575

TAB. 7

The dynamics of immunological indices in patients of the experimental group at the start and end of treatment.

INDICES	NORMAL VALUES	AT THE TREATMENT'S START			AT THE TREATMENT'S END		
		HVBC n=6	HVCC n=8	HVBC+HVCC n=2	HVBC n=6	HVCC n=8	HVBC+HVCC n=2
Leukocytes (10^9/l)	4,5-8,0	5.6±0,700	5,775±0,480	5,55±1,15	5,5±0,705	4,937±0,546	5,15±0,85
Lymphocytes (%)	22-38	34,333±2,333	35.625±2,87	40±7	39,333±4,247	36,125±2,247	34,5±4,5
Lymphocytes (10^9/l)	1,2-2,4	1,961±0,230	2,081±0,254	2,13±0,07	2,205±0,405	1,812±0,245	1,75±0,05
Lymphocytes Ta (%)	20-34	15.333±2,788	17,25±1,655	15,5±3,5	13,166±2,056	14,75±1,760	18,5±8,5
Lymphocytes Ta (10^9/l)	0,3-0,7	0,288±0,036	0,366±0,060	0,345±0,045	0,338±0,089	0,272±0,042	0,35±0,15
Lymphocytes Ttot (%)	55-75	42,666±4,038	37,125±1,949	41±2	34,666±3,938	34,875±3,943	39,5±9,5
Lymphocytes Ttot (10^9/l)	0,9-1,5	0,873±0,147	0,781±0,101	0,85±0,05	0,823±0,197	0,687±0,125	0,7±0,2
Lymphocytes Tterm (%)	0-5	0,666±0,494	0,5±0,5	1±1	0,166±0,372	0	0
Lymphocytes Tterm (10^9/l)	0-0,09	0,013±0,011	0,015±0,015	0,02±0,02	0,001±0,001	0	0
Lymphocytes TFR-E-RFC (%)	38-58	30,166±2,676	26,125±2,614	26,5±0,5	24,833±2,903	22,25±2,403	30±9
Lymphocytes TFR-E-RFC (10^9/l)	0,7-1,1	0,595±0,092	0,551±0,088	0,575±0,025	0,586±0,132	0,433±0,085	0,55±0,15
Lymphocytes TFS (%)	12-28	12,5±1,979	11,25±1,221	14,5±2,5	9,833±1,777	12,625±2,419	9,5±0,5
Lymphocytes TFS (10^9/l)	0,23-0,43	0,255±0,052	0,226±0,041	0,305±0,065	0,231±0,062	0,238±0,059	0,165±0,015
Lymphocytes EAC-RFC (%)	9-18	21,666±2,333	22,25±2,160	24,5±4,5	16,166±3,070	18,375±4,597	24,5±0,5
Lymphocytes EAC-RFC (10^9/l)	0,18-0,32	0,43±0,074	0,456±0,060	0,525±0,115	0,356±0,076	0,361±0,107	0,43±0,02
CIC (U.E.)	≤ 60	46,333±2,564	54,125±12,99	80±15	55,666±14,061	90,375±27,56	38,5±31,5
LTL	4-7	7,066±0,828	8,168±0,99	6,5±1	7,8±0,977	8,125±0,909	7,65±0,95
T/B	2,0-5,0	2,191±0,442	1,768±0,171	1,725±0,225	2,483±0,406	2,731±0,539	1,605±0,355
TFR/TFS	2,0-4,0	2,988±1,336	2,668±0,538	1,875±0,375	3,058±0,858	2,017±0,302	3,1±0,8

TAB. 8

The dynamics of immunological indices in patients of the control group at the start and end of treatment.

CONCLUSIONS

The combined treatment with Citomix™ + Guna®-Liver + Interferon gamma 4C had contrubuted to:

1) the amelioration of clinical symptomatology in patients with HVBC, HVCC and HVBC+HVCC;
2) the liver and spleen dimensions had normalised in all patients, from the experimental groups, but more frequently in patients with HVBC (over 50% of cases) compared with patients from the control group. Hepatomegaly and splenomegaly were found in patients of the control group with the same frequency before and after treatment;
3) there was a moderate decrease of the cytolysis index values (ALAT, ASAT);
4) a seroconversion was established in the AgHBs system in 2 of the 8 patients with HVBC and in 1 of the 2 patients with HVBC+HVCC;
5) the formation of anti-HBs (protective antibodies) compared with AgHBs in 3 patients suggests to us that these medicines probably possess antiviral capabilities.

- Anti HVC IgM had been revealed with the same frequency in patients with HVCC both at the start and the end of treatment;
- An improvement in immune status was found which was more marked in patients with HVCC. ■

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