

G. Nagy



CLINICAL

SUMMARY

This study concerns the evolution of 11 patients with hepatitis C under treatment with Interferon alpha 4C, Interferon Gamma 4C, Interferon gamma 30 C for a period of 6 months. The evaluation is based on the clinical evolution as well on lab tests. It was taken into consideration the presence of the markers for hepatitis C, AB anti HCV (EIA) qualitative and HCV - RNA quantitative (real-time CPR), at the beginning and end of treatment. The dynamic evolution of biochemical tests reflecting the liver functional state. The biochemical tests considered: GOT, GPT, gamma GT, total and fractional bilirubin and proteins. In 9 cases a significant reduction of the quantitative presence of marker (HCV - RNA quantitative - real time CRP) (eg: at 2,650,000 / ml to 95,000 / ml) was obtained. In the majority of the cases, one month after the beginning of the treatment an improvement has been registered in the biochemical indices that reflect the liver function.

According to the principles of PRM, the association of the therapy with Interferon alpha 4C, Interferon gamma 4C with homotoxicologic detoxifying treatment for the change of the treatment with Interferon gamma 30CH has led to normalization of biochemical tests in 8 cases in the following 2 months.

We consider very interesting the liver reactivity at the beginning of the treatment expressed by biochemical tests which seem to indicate an initial aggravation. That may suggest the immediate effect of the treatment with Interferon gamma 4C, on one hand, on the other hand, the PRM concept to integrate this treatment with a general psycho-neuro-immuno-endocrine rebalancing therapy.

- It is presented a detailed analysis of the evolution of two cases where the results show the evident efficiency of the treatment after 3 and 6 months.

The final proposal is to initiate a web forum for patients treated with Interferon gamma 4C, 30C where they can share the results, their experience encouraging others to choose this efficient, non aggressive treatment.

KEY WORDS

HEPATITIS C, INTERFERON ALPHA 4C, INTERFERON GAMMA 4C, INTERFERON GAMMA 30 C, HEPATIC FUNCTION, PRM

INTERFERON ALPHA 4C AND INTERFERON GAMMA 4C: THEIR THERAPEUTIC SYNERGY IN LIVER PATHOLOGIES ACCORDING TO PHYSIOLOGICAL REGULATING MEDICINE

"A different point of view is simply a view from a place where you were not."

- In spite of tremendous progress in virology and molecular biology, at the beginning of the millennium, liver pathology still remains the 6th leading cause of mortality.

There are an increasing number of new drugs for potential use in liver diseases and though they will undoubtedly improve results, there are still significant limitations in the treatment of liver pathologies. It is necessary to find new solutions to improve the treatment methods for hepatic diseases.

Currently, there are no effective therapies available for patients with chronic hepatitis C who have failed to respond to optimal interferon alpha-based treatments.

Chronic hepatitis C is the major cause of chronic liver diseases, cirrhosis, and liver cancer in most of the Western world. It affects approximately 4.2 million Americans, and more than 200 million people worldwide are infected with HCV. In Romania, the prevalence

of anti-HCV (around 5%) prior to the introduction of routine screening was 10 times higher than in Western European countries.

The hepatitis C virus (HCV) is a serious health concern and an important cause of chronic liver disease, leading to cirrhosis and hepatocellular carcinoma in humans. Of particular concern is that the virus establishes a chronic infection in 85% of cases (FIG. 1) and that there are no specific and broadly effective anti-HCV compounds to date. Belonging to the *Flaviviridae* family, HCV is a single-stranded RNA virus of positive polarity (FIG. 2) encoding a single polypeptide chain that is cleaved co- and post-translationally into both structural (core, E1, E2, p7) and non-structural (NS2, NS3, NS4A, NS4B, NS5A, NS5B) proteins (reviewed in Reed and Rice, 2000).

The hepatitis C virus NS2/3 protein is a highly hydrophobic protease responsible for the cleavage of the viral polypeptide between non-structural pro-

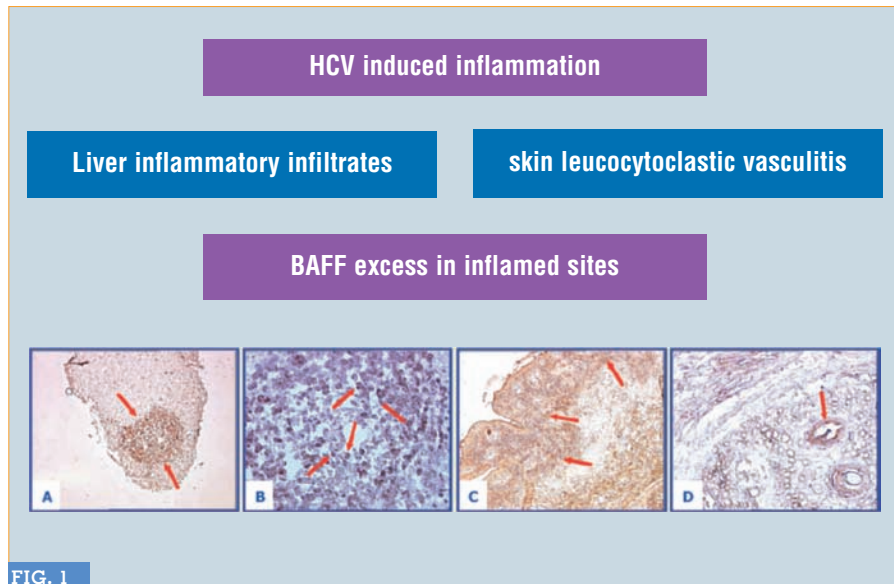


FIG. 1

HCV-induced inflammation mechanism.

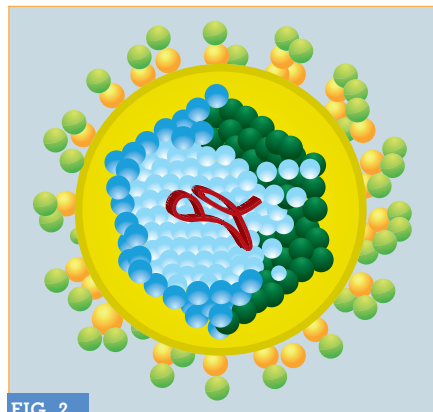


FIG. 2

Hepatitis C Virus.

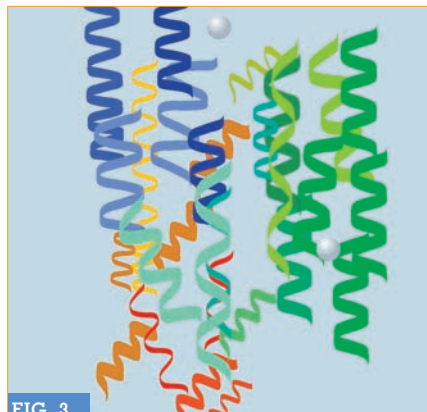


FIG. 3

Interferon alpha.

teins NS2 and NS3. However, many aspects of the NS2/3 protease's role in the viral life cycle and mechanism of action remain unknown. Based on the recently elucidated crystal structure of NS2, NS2/3 has been proposed to function as a **cysteine protease** despite its lack of sequence homology to proteases of known function. In addition, although shown to be required for HCV genome replication and persistent infection in chimpanzee, the role of NS2/3 cleavage in the viral life cycle has not yet been fully investigated. However, several recent studies are beginning to clarify possible roles of the cleaved NS2 protein in modulation of host cell gene expression and apoptosis.

The role played by hepatitis C virus (HCV)-specific immune responses in the outcome of HCV infection is incompletely understood. Because HCV is believed to be noncytopathic, **the immune response has been thought to play a key role in the hepatic damage and ensuing fibrosis that occurs during chronic infection.** However, accumulating data from multiple laboratories have indicated that there is an association between enhanced HCV-specific T cell immunity and both recovery from acute infection and antiviral therapy-induced viral clearance. These data suggest that vigorous and broad-based HCV-specific T cell immunity is beneficial to the host and favors viral clearance.

ALLOPATHIC TREATMENT

The Interferons are a group of protein immunoregulators synthesized by T lymphocytes, macrophages, fibroblasts and other types of cells, after stimulation with viruses, antigens, mitoses, DNA, etc.

Interferon increases the ability of macrophages to destroy tumor cells, viruses and bacteria.

They are classified as **alpha, beta and gamma**, with the latter also being referred to as immune-Interferon.

What studies point out about the allopathic treatment.

Interferon alpha (FIG. 3) was approved as a therapy for hepatitis C in 1991. However, the overall rate of sustained virologic response, defined as the absence of HCV RNA in serum at least 6 months after the discontinuation of therapy, is low (generally <20%) with Interferon alpha monotherapy.

The subsequent addition of the oral antiviral agent *Ribavirin* to Interferon led to a marked improvement in rates of sustained virologic response (40 to 45%). *Ribavirin* alone lowered serum enzyme levels but had little effect on HCV RNA levels.

- The most recent important advance in the treatment of hepatitis C was the development of a long-acting Interferon, *pegylated Interferon* (pegInterferon), produced by the covalent attachment of polyethylene glycol to the Interferon molecule. With its increased half-life, pegInterferon can be given as a weekly dose. In two large trials, the rates of sustained virologic response to a 48-week course of pegInterferon and *Ribavirin* were 54 and 56%, as compared with 44 and 47% with standard Interferon and *Ribavirin* and only 29% with pegInterferon alone. Response rates were higher among patients with genotype 2 or 3 than among those with genotype 1. A subsequent trial of different regimens of pegInterferon alpha-2a and *Ribavirin* showed that patients

with genotype 2 or 3 could be treated with a lower dose of *Ribavirin* (800 mg rather than 1000 to 1200 mg daily) and that the rates of sustained virologic response after 24 weeks of therapy (81 and 84%) were similar to the rates after 48 weeks of therapy (79 and 80%).

Therapy is recommended for adults with chronic hepatitis C who have detectable HCV RNA in serum, elevations in aminotransferase levels, histological evidence of progressive liver disease, and no other serious coexisting conditions or contraindications. Specific qualitative assays for HCV RNA are available that have a lower limit of sensitivity of 10 to 50 IU (approximately 40 to 100 genome equivalents) per milliliter. In addition, HCV RNA can be quantified; most patients with chronic infection have HCV RNA levels between 0.2 and 5 million IU (approximately 1 to 20 million genome equivalents) per milliliter.

- An elevated serum alanine aminotransferase level is one of the criteria for instituting therapy because most persons with normal alanine aminotransferase levels have mild, nonprogressive disease. However, the degree of elevation does not always reflect the severity of disease and is not predictive of a patient's response to therapy. Thus, normal aminotransferase levels should not exclude patients from therapy. *In vitro* studies demonstrate that exposure of primary neuron cultures of mice to Interferon alpha has the effect of loss of dendritic arborisations which becomes more obvious as the dose of Interferon is increased, resulting in permanent neuronal damage.

Conclusions about the antiviral activity of allopathic Interferon alpha and gamma.

The antiviral effects of Interferon gamma have been assessed in several small studies in chronic viral hepatitis, but mostly in chronic hepatitis B. In a study of hepatitis B, Interferon gamma had similar effects to Interferon alpha

PROTOCOL

Interferon gamma 4C:
20 drops x 3/day, for 3 months

Interferon gamma 30C:
20 drops x 3/day, for 3 months

Analisi	Risultato	Unità	Valori di Riferimento	Uomini
Esame del: 30/06/08				
Chimica Clinica				
GLICEMIA BASALE Color.	77 mg/dl	da	60	a 110
GOT Cinetico-spettof.	36 U/l	da	0	a 40
GPT Cinetico-spettof.	48 U/l	da	0	a 30
GAMMA GT Cinetico Spettof.	157 U/l	da	15	a 60
BILIRUBINA TOTALE E FRAZIONATA				
SODIO Spetrofotometrico	141 mEq/l	da	135	a 150
POTASSIO spettofotometrico	4.1 mEq/l	da	3.6	a 5
BILIRUBINA TOTALE	0.88 mg/dl	da	0.2	a 1.1
BILIRUBINA DIRETTA	0.12 mg/dl	da	0.1	a 0.4
BILIRUBINA INDIRETTA	0.76 mg/dl	da	0.15	a 0.8
Ematologia				
ES. EMOCROMOCITOMETRICO Ematologia	Vedi allegato			
Markers Epatite C				
HCV- RNA QUANTITATIVO* Real Time PCR	95.000.000 copie/ml - 23.700.000 UI/ml	Limite inferiore di sensibilità: 500 UI/ml		

Questo laboratorio partecipa al sistema V.E.Q. (valutazione esterna di qualità) Le analisi con asterisco sono eseguite in service presso il Centro BIANALISI S.r.l. via Russolillo, 63 00138 Roma

ActaLab -2000- Licenza N. AL60300410133 Stampato il: 10/07/08

Beginning of the treatment with INTERFERON γ ch4, for 2 month than INTERFERON γ 30ch, 15 drops x 3 times daily, long term

Case No. 1

Lab tests (before the treatment).

on serum levels of HBV DNA polymerase, but therapy for up to 6 months was poorly tolerated and did not lead

to sustained remissions in disease. Furthermore, when administered together, there was no evidence of synergy

Allopathic Interferon treatment is not for everyone.

Interferon therapy is not for everyone. The presence of other medical conditions may affect the use of Interferon alpha. Bleeding problems, convulsions, history of mental problems (depression), diabetes, heart disease, kidney disease, lack of blood supply to any part of the body, lung disease, thyroid disease, autoimmune disease (problems with overactive Immune System).

Lab tests should be done at least once a month to monitor any abnormalities within the white blood cells, the platelets, and the red blood cells. Also, Interferon should not be used by pregnant women because it is not known whether Interferon alpha will be harmful to an unborn baby. In addition, it is not known whether Interferon passes into breast milk. This medication should not be used during breast-feeding.

Absolute contraindications.

- Pregnancy
- Breast-feeding
- Allergy to either drug.

Relative contraindication

Decompensated liver disease, ascites, bleeding esophageal varices, hepatic encephalopathy, major neuropsychiatric disease, coronary or cerebrovascular disease, renal failure, history of solid organ transplantation, alcohol abuse, anaemia, thrombocytopenia, or leucopenia, renal dysfunction.

Adverse effects.

Side effects of classical treatment affect virtually all patients who receive it. The most common adverse effects are muscle aches and fatigue, but more difficult to manage are the psychological side effects such as depression, anxiety, irritability, and sleep. Haemolysis and anaemia are the major

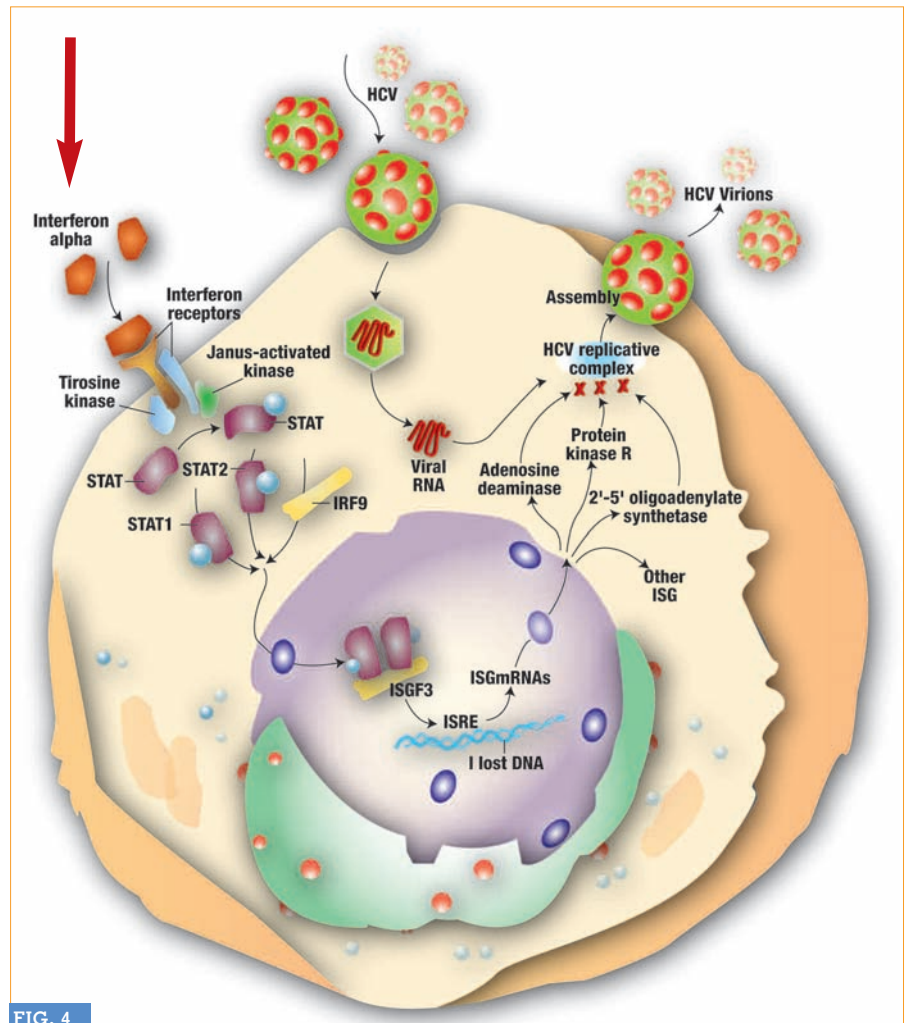


FIG. 4

The possible mechanism of Interferon alpha.

The NEW ENGLAND JOURNAL of MEDICINE (med 355; 23, December 7, 2006). Massachusetts Medical Society.

reasons for dose reduction. The stress of the sudden onset of anaemia can induce myocardial infarction in persons with pre-existing coronary disease or stroke in those with cerebrovascular disease. *Ribavirin* is also teratogenic and strict adherence to an effective means of birth control is mandatory for both women and men who receive this drug. Serious side effects of combination therapy occur in 1 to 2% of patients and permanent injury and death can occur.

► *The New England Journal of Medicine 2006. Massachusetts Medical Society "The cost of a 48-week course of peginterferon and Ribavirin ranges from \$30,000 to \$40,000, depending on local charges and the dose and brand of*

drugs used. The expenses for monitoring and physician visits also need to be considered in weighing the costs of the therapy."

WHY INTERFERON LOW DOSE ?

Physiological Regulating Medicine in accordance with informational medicine, uses **homeopathic cytokines** as initiating the Neuro-Immuno-Endocrine Reprogramming.

- Low dose action mechanism (homeopathic cytokines activate some units of cellular or plasmatic receptors in the same dilution as these substances work physiologically 10⁻⁶ – 10⁻⁹), through an UP-REGULATION mechanism.

- Affinity and redundancy [biological effect with minimal ligand concentration – only a small fraction (10%) of the receptors need to be occupied to get a large (50%) response].
- PRM proposes a general action that is non-toxic and multi-level without any contraindications or side effects, enabling the Immune System to express its whole potential.
- It doesn't substitute the Immune System, doesn't force or block it, just informs in a soft way.
- It's compatible and synergic with any other treatment, being situated borderline between conventional and non conventional medicine.
- Produced by bio-technology, recombinant DNA.
- Assumptions of Arndt – Schultz's Law.
- Efficiency.
- Could be used in all cases when allopathic interferon is not indicated.
- Very low costs.

A possible mechanism of action of low dose Interferon alpha.

As we see, the initiation of the chain of reactions is determined **qualitatively not quantitatively**. The mechanism of action of the homeopathic cytokines (Interferons) consists of the sensitization or activation of some of the units of cellular or plasmatic receptors. *Low doses* of $10^{-6} - 10^{-9}$ work the same as these substances work physiologically.

According to Physiological Regulating Medicine, the response of a cell to a messenger depends on the number of receptors occupied. Only a small fraction (10%) of the receptors need to be occupied to get a large (50%) response.

According to *the New England Journal of Medicine* 355123 (2006, Massachusetts

PROTOCOL

Interferon gamma 4C

20 drops x 3/day, for 3 months

Guna®-Matrix

20 drops x 3/day

Guna®- Liver

5 pellets x 3/day

Eubioflor 1

20 drops x 3/day

I.B.I. "Dr. Matei Bals", Bucuresti **GENETICA MOLECULARA**

Buletin de analize medicale

Data setului de analize 21.06.2007 11:56

Recoltat la data de: Validat la data de: 29.06.2007 09:3

Set lucrat de: Cod set AD3477

Nume: Varsta: 48 Medic:

Prenume: Cod prezentare: 701354

C.N.P.: 1590108400087 Nr. FO: 74627 / 07 Departament SECTIA ZI ADULTI

Urgenta NU

Teste Cantitative

Test	Rezultat	Val. norm./unit. mas.
HCV-RNA Cobas TaqMan	2070000	<2.80E+01 ->1.4E+09 / U/mL

Lucrat de: genetica user

La inceputa trat. cu Interferon Gamma 20 cdt.

Tiparit de: Data tiparii 17.07.2007 14:30 pag. 1 / 1

Case No. 2

Lab test (before the treatment).

Medical Society) a mechanism of action of Interferon alpha could be the following: Interferon alpha (FIG. 4) engages receptors on the hepatocyte cell-surface membrane, causing them to dimerize and to activate Janus-activated and tyrosine kinases that phosphorylate the cytoplasmic signal transducers and activators of transcription (STAT) proteins. STAT1 and STAT2 dimerize and bind Interferon regulatory factor 9 (IRF9), creating a large complex (Interferon-stimulated gene factor 3, or ISGF3) that is translocated into the nucleus, where it binds to Interferon-stimulated response elements (ISREs) on DNA. This engagement causes the

transcription of multiple (>100) Interferon-stimulated gene (ISG) mRNAs, which exit the nucleus and encode proteins that alter cell metabolism and interfere with virus replication, protein synthesis, and assembly. Major ISGs thought to be important in inhibiting HCV replication include 2',5' oligoadenylate synthetase, which activates antiviral RNases; RNA-specific adenosine deaminase, which edits viral RNA; and protein kinase R, which inactivates protein translation from viral mRNA. The HCV replicative complex is associated with the cytoplasmic membranes of hepatocytes and comprises RNA replicative

intermediates, viral mRNA, structural and nonstructural viral proteins, and assembling virions.

A possible mechanism of action of Interferon alpha low dose.

This study was designed to assess the antiviral activity of Interferon alpha and gamma in homeopathic doses (4C, 30C) in patients having anti-HCV in serum, and having HCV RNA in levels above 10,000 IU/ml.

The dynamic of clinical evolution and lab tests of the patients following the association of this treatment with detoxification and drainage using the PNEI concept.

Analiza	Um	Rezultat	Valori biologice de referinta		Incadrare
			Minim	Maxim	
Glicemie	mg/dl	119.00	70	115	(-----)*
TGO	U/L	32.00	0	37	(----*)
TGP	U/L	63.00	0	40	(-----)*
Trigliceride serice	mg/dl	151.00	0	200	(---*)
Acid uric seric	mg/dl	6.46	3.4	7	(-----)*

Responsabil de analiza

Teste coagulare					
Fibrinogen seric	mg/dl	320	200	400	(--*--)

Responsabil de analiza

Serologie	
Ac HCV	PREZENT
Proteina C reactiva	ABSENTA < 6 mg/l

Responsabil de analiza

Informatii despre serviciile oferite la: www.drnicoaumaria.webcad.ro, sugestii si reclamatii la: drnicoaumaria@yahoo.com
Analizele s-au efectuat conform procedurilor specifice: PS-01B, PS-02, PS-03B, PS-03F, PS-03D, PS-03E, PS-16, PS-12, PS-14, PS-15C, PS-15D.

Medic:

Interlink: Suport Informativ asigurat de SC Medical Robotics SRL, tel. 0788 369 831. Toate drepturile rezervate

Case No. 2

Lab test (before the treatment).

PATIENTS AND METHODS

Selection of patients:

Eleven patients were enrolled including 7 women and 4 men with ages between 32 and 62 years old, with **chronic HCV infection** with a detectable serum HCV RNA level.

- 2 patients also had HIV infections
- 1 hepatocellular carcinoma
- 2 were non-responders to a previous therapy with Interferon alpha and Ribavirin.

PROTOCOL OF THERAPY

■ **Interferon alpha 4C** for 3 months alternated with **Interferon gamma 4C** for 3 months (20 drops x 3/day).

■ 6 patients were given drainage and detoxification treatment:
 - **Guna[®]-Matrix + Eubioflor[®]**, 20 dps x 3/day + **Guna[®]-Liver** 5 pellets x 3/day.

■ For the patient with hepatocellular carcinoma: **Guna[®]-Rerio** (20 drops x 3/day).

La 3 luni de la inceperea trat. cu Interferon Gamma 30CH.

INSTITUTUL NATIONAL DE BOLI INFECTIOASE "DR. MATEI BALS"
 str. Dr. Grozovici nr. 1 sector 2, Bucuresti

Clinica _____

BULETIN DE ANALIZĂ
 25. 03.2008

REZULTAT

NUME ȘI PRENUME _____ SEXUL M/F _____

Examenul cerut HCV-RNA

Rezultatul analizei _____

HCV-RNA REAL TIME PCR
M2000 RT (ABBOTT)

1.112.935 ui/ml.

Lucrat de: _____

Tipărit la SC GRAFOPRESS Tel./fax: 0242-314647

Case No. 2

Lab test (after 3 months of treatment).

CLINICAL STUDY DESIGN

Patients underwent an initial evaluation that included a medical history and physical examination, a battery of blood tests, and a quantitative determination of serum HCV RNA and CRP in real time.

Patients were stratified according to previous response or combined pathology (responders or relapses to Interferon alpha, other associated diseases), protocol was modified according to pathology.

The primary endpoint of this study was a decrease of HCV RNA levels by one log or more during treatment as detected by quantitative CRP as well the improvement of the functional state of liver (normalizing of biochemical lab tests).

RESULTS

■ In **9 cases** a significant reduction of the quantitative presence of marker (HCV – RNA quantitative – real time CRP) was obtained.

■ In the **majority of cases**, one month (or two) after the beginning of the treatment there was a visible increase in biochemical indices that reflected liver function aggravation.

■ After **6 months** of treatment in 8 cases, the lab tests were improved.

Lab tests of two clinical case are presented (**Case No1**, **Case No2**).

CONCLUSIONS

- Even in *low doses*, the homeopathic cytokines (Interferon alpha and gamma) have demonstrated effectiveness in the complementary treatment of hepatitis C, decreasing HCV RNA levels.

In addition, the initial aggravation of biological tests demonstrates the action of the treatment.

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Sector 2, Bucuresti

Nr. *La 6 luni de la inceperea trat. cu Interferon Gamma 30 CH.*
Data recoltari

BULETIN DE ANALIZA

SR
ISO 9001

Clinica: LAB. GENETICA

Nume si prenume: _____

Examenul cerut: HCV - RNA
HCV - RNA REAL TIME PCR M₂₀₀₀ RT (ABBOTT)

Rezultatul analizei:

12.635 ui/ml

Lucrat de: _____

Medic sef de laborator,

Case No. 2

Lab test (after 6 months of treatment).

Association of detoxification and drainage rebalancing the liver functions, significantly improving the laboratory tests (gamma GPT). ■

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PHYSIOLOGICAL REGULATING MEDICINE







USES

For the temporary relief of symptoms due to: **Post surgery recovery, Tonsillitis, Childhood illnesses, Tender lymph nodes.**

DIRECTION

Adults and Children 6 years and over: 10 drops 3 times a day in a little water.
Children 6 years and under: ½ adult dosage.
 Take 15 minutes before meals.

MOST COMMON COMBINATIONS

Patients with good liver function	Guna-Lympho + Guna-Matrix + Guna-Liver
Patients with good bowel function	Guna-Lympho + Guna-Matrix + Guna-Bowel
Patients with good kidney function	Guna-Lympho + Guna-Matrix + Guna-Kidney
Venous insufficiency with lymphatic stasis	Guna-Lympho + Guna-Vein
Trauma with serious extravasations; hydrarthrosis	Guna-Lympho + Guna-Trauma
Lymphadenopathies	Guna-Lympho + Guna-Tonsil

INGREDIENTS

Active ingredients:
 Apis mellifica 8X HPUS, Calendula officinalis 1X HPUS, Capillary tissue 6X, DLmalic acid 6X, Equisetum hyemale 3X HPUS, Fumaricum acidum 6X HPUS, Graphites 6X, 12X, 30X, 200X HPUS, Hydrastis canadensis 1X HPUS, Hydrocotyle asiatica 1X HPUS, Juglans regia 3X HPUS, Levothyroxin 6X, 12X, Lymphatic vessel 6X, Magnesia phosphorica 6X, 12X, 30X, 200X HPUS, Myosotis 3X HPUS, Natrum oxalacetikum 6X HPUS, Nat pyr 6X HPUS, Phytolacca decandra 3X HPUS, Sarsaparilla 3X HPUS, Taraxacum officinale 1X HPUS, Trichinoyl 6X, Vein 6X.

Inactive ingredient: Ethyl alcohol 30%

PACKAGE SIZE

30 ml / 1.0 fl. oz. bottle