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The Influence of Steatosis and Conjugated Factors on the Response to Antiviral Therapy in Chronic Hepatitis Band C

PhD Thesis Advisor
Doina Cârstea PhD,Professor

PhD Student
Alice Elena GĂMAN

CRAIOVA

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Contents

Keywords

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INTRODUCTION

Viral hepatitis is one of the greatest problems of infectious pathology due to the high incidence of acute infections, the risk of chronicity, severity of chronic infections and the costs of these diseases. Hepatitis is an acute or chronic liver inflammation that can be caused by alcohol, drugs, autoimmune diseases, metabolic diseases and viruses.

The Evolution of liver disease to chronicity is performedby worsening and persistence of initial injuries triggered by etiologic factors.In the evolution of liver disease, it is important the regular monitoring and the comparison of clinical and paraclinical parameters for defining a diagnosis of certainty.

The presence of viral or immunological markers in the serum of patients is important to assess the ethology, level of activity, and behaviour therapy.

Hepatitis B virus (HBV) is a noncytopathic virus and the severity of diseases associated with HBV infection is considered to be related to the intensity of the host immune response to the virus. Thus, the cellular immune response appears to be the main arm involved in the pathogenesis of the disease.

The presence of the hepatitic virus C (HCV), besides the severe impact on the life style and lingering symptomatology, predisposes towards a risk of evolution of pathogenic process and the development of complications. Among those, are numbered the hepatitis viral C cirrhosis and the hepatocellular carcinoma, with a guarded prognostic and a high mortality rate. Currently it is accepted that approximately 3% of the global population is affected by HCV, with chronic infection in the case of 170 million people.

The goals of the treatment of the chronic viral hepatitis C are represented by the reduction of the mortality rate by stopping the evolution of the chronic hepatitis towards the complication stage and implicitly, towards hepatocellular carcinoma, the elimination and the persistent suppression of the viral factor, aspects proved trough the negativity of the viral markers in circulation, the normalization of biochemical parameters, the reduction of the hepatic inflammatory process and the prevention of complications and also the improvement

of life quality. At the moment, the interferons and the nucleoside analogues are recognized and utilized as effective antiviral agents in the treatment of chronic viral hepatitis.

Favourable response to antiviral therapy is influenced by such predictive factors as NASH, insulin resistance, liver fibrosis and certain biochemical parameters, especially ALT, AST.

The severity of steatosis plays an important role in the development and progression of fibrosis liver damage. Steatohepatitis is now regarded as an important cause of cirrhosis of unknown origin or as final stage of some liver lesions.

In the pathogenesis of NASH (non-alcoholic steatosis) are involved insulin resistance, excess of fatty acids in hepatocytes, lipid peroxidation and oxidative stress. Lesion progression to cirrhosis is variable, but usually slow.

NASH is commonly associated with central and visceral obesity, insulin resistance, hyperglycaemia and hypertriglyceridemia. Difficulties encountered in the diagnosis and treatment of this condition are linked to the lack of knowledge about the pathogenic mechanism so that identification of the factors responsible for the transformation of hepatic steatosis to steatohepatitis and cirrhosis are the final target of many studies.

The main goals of this study are to evaluate biological response rates, sustained viral response and to identify the factors predictive of a favourable response to antiviral therapy in patients with chronic hepatitis B and C.

LITERATURE REVIEW

CHAPTER 1

VIRAL HEPATITIS

In the first chapter are presented the general characteristics, epidemiology and pathogenesis of viral hepatitis beginning with classical view to the latest data from the specialty literature. Also is thoroughly described the diagnostic of viral hepatitis B and C, emphasizing biochemical tests, serological tests and liver biopsy.

CHAPTER 2

PRINCIPLES AND METHODS OF TREATMENT IN CHRONIC VIRAL HEPATITIS

In the second chapter we conducted a review of all currently known therapeutic methods in the treatment of chronic viral hepatitis. The main goals of the therapy of chronic viral hepatitis are represented by the elimination or suppression of hepatitis viruses, the amelioration anti-inflammatory and immunological changes, regression and stop liver damage, stimulate liver regeneration and combating accompanying clinical manifestations.

CHAPTER 3

METABOLIC SYNDROME

Metabolic syndrome is a combination of risk factors of metabolic origin that is accompanied by an increased risk of type 2 diabetes and cardiovascular diseases. According to the results of epidemiological studies, the increasing obese subjects resulted in increased prevalence of metabolic syndrome.

In this chapterare presented concepts, clarification of the association of risk factors, pathogenesis diagnosis and strategy components of the metabolic syndrome. We have shown an association between metabolic syndrome and obesity, key mediators of the relationship between the two entities being adipokines, synthetic products by the adipose tissue with both direct and indirect effects in the regulation of appetite, the carbohydrate metabolism, lipid and protein and inflammatory process.

CHAPTER 4

NON-ALCOHOLIC STEATOSIS

Non-alcoholic hepatic steatosis is currently regarded as the hepatic manifestation of metabolic syndrome characterized by a significant deposition of lipids in hepatocytes and occurs in patients who do not consume substantial quantities of alcohol. Non-alcoholic hepatic steatosis is currently the most common chronic liver disease.

Epidemiological studies confirm the large variations in regard to the incidence and prevalence reported, NASH being diagnosed in about 11-15% of patients who have undergone liver biopsy. In obese patients the prevalence is 19% and only 2.7% for those thinner. In this chapter is also presented the ethology and pathogenesis of NASH, the association of decreased insulin sensitivity and metabolic syndrome, and not least the diagnosis of NASH.

PERSONAL CONTRIBUTIONS

OBJECTIVES. CASUISTRY AND METHODOLOGY

The objectives of the research were:

1. *The main objectives*

- Evaluation of biological response rates and sustained virological response in patients with chronic hepatitis C treated with α-IFN, PEG-IFN α-2a or α-2b plus Ribavirin.
- Evaluation of biological response rates and sustained virological response in patients with chronic hepatitis B treated withPeg-IFN α -2a/b.
- The identification of predictive factors for a favourable response to antiviral therapy in patients with chronic hepatitis C.
- The identification of predictive factors for a favourable response to antiviral therapy in patients with chronic hepatitis B.

2. *The secondary objectives*

- Development of non-invasive methods for the assessment and quantification of inflammation and liver fibrosis.
- The study of factors involved in the progression of steatosis to steatohepatitis and cirrhosis.
- Identify metabolic changes and insulin resistance.

The research is performed within the Internal Medicine Clinic of Filantropia University Hospital, in 2010-2013. There were selected to take part to the research 376 patients who have fulfilled all inclusion and exclusion criteria. These treatment-naive patients with chronic HBV or HCV were divided into 2 groups.

Group 1 - consisting of 210 patients with chronic HCV treated with:

Pegylated interferon α2a 180μg/week + ribavirin: 1000 mg/day body weight <75 kg; 1,200 mg/day body weight>75 kg or pegylated interferon α2b 1.5 mg/kg/week + ribavirin: 1000 mg/day weight bodyweight <75 kg; 1,200 mg/day for body weight>75 kg

Group 2 - consisting of 166 patients with chronic HBV treated with:

Pegylated Interferon α-2a: 180 mcg/week; duration of therapy: 48 weeks

There were several criteria for inclusion and exclusion of subjects included in this study:

CHRONIC HEPATITIS C – NAIVE PATIENTS:

The inclusion criteria:

• Biochemical: normal or elevated ALT;

• Virologic: HCV RNA detectable.

• Histologically: liver biopsy, FibroMax: A ≥ 1, F ≥ 1 and / or S ≥ 1, Fibroscan> 1

• Age ≤ 65 years,> 65 years will be evaluated based on comorbidities therapeutic risk

The exclusion criteria:

Are excluded from interferon therapy patients with: neurological diseases, psychiatric illnesses, decompensated diabetes, autoimmune diseases, ischemic heart disease or uncontrolled severe heart failure, uncontrolled severe respiratory disorders, Hb<11g/dL, bnumăr of leukocytes <5,000 / mm3, number of neutrophils <1,500 / mm3.

CHRONIC HEPATITIS B – NAIVE PATIENTS

HbeAgpositiv - Chronic hepatitis B:

The inclusion criteria in treatment:

• Biochemical: ALT ≥ 2 x N

• Virological: HbsAg positive, HBeAg positive and antiHBe negative; antiHVDIgG negative; HBV DNA ≥ 20,000 IU / ml.

• assessment of fibrosis and necroinflammatory activity by PBH or FibroMax;

- Patients with the above criteria do not require the assessment of fibrosis and necro-inflammatory activity;

- In patients with ALT <2xN and age> 40 years, or FibroMax performing liver biopsy and treat if significant disease;

The exclusion criteria:

- Coinfection with HIV, HCV or HDV;

- Previous antiviral treatment for any length of time;

- Other chronic liver diseases (chronic alcoholism, Wilson disease, NASH, NAFLD) liver cirrhosis, history of ascites, variceal bleeding, hepatic encephalopathy, and other conditions suggesting decompensated liver disease, fasting plasma glucose> 120 mg / dl; neoplasia diagnosed or treated in the last 5 years, patients treated with corticosteroids or immunosuppressants in the last 30 days, or if they are expected to also administer medications during the study, known allergies to antiviral medications.

HbeAg negative - Chronic hepatitis B:

The inclusion criteria:

- Biochemical: ALT ≥ 2 x N
- Virological: HBsAg positive, HBeAg negative and antiHBe positive; antiHVDIgG negative, HBV DNA ≥ 2,000 IU / ml.
- assessment of fibrosis and necroinflammatory activity by PBH or FibroMax

THE ANALYZED PARAMETERS

1) **Demographic data: age, sex**

2) **Anthropometric data**: weight, height, body mass index - BMI, calculated by the formula - BMI = W/H2 where W (weight) was expressed in kilograms and H (height)

in meters. Subjects according to BMI classification was as it follows: normal weight - BMI <25 kg/m2, overweight - BMI = 25-29.9 kg/m2, obese - BMI ≥ 30 kg/m2.

3) Laboratory tests

- **Biochemical Tests**: We used standard procedures to ensure the reproducibility of the following parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST) by spectrophotometric method, fasting glucose by spectrophotometric method, fasting insulin by hexokinase method, total cholesterol (TC) and triglycerides (TG) by spectrophotometric method. We determined serum iron (Fe/kg) by spectrophotometric method and also serum ferritin by electrochemiluminescence method (ECLIA). Iron-loading plays a role in the pathogenesis of NASH, as demonstrated association between metabolic syndrome and iron overload in producing liver disease. They established on fresh serum using a Hitachi 917 autoanalyzer.
- **Assessment of insulin sensitivity**: We determined insulin sensitivity using HOMA-IR (homeostasis model of insulin resistance) using the following formula: fasting plasma glucose (mg/dl) x fasting insulinemia (μU/ml) / 405.
- *Diagnostic tests for the detection of HCV infection:*

  I – Serological assays – detect antibody to hepatitis C virus (anti-HCV) by Enzyme-linked immunosorbent Assay (ELISA)

  II - Molecular assays - detect, quantify and/or characterize HCV RNA. Detection of HCV RNA by polymerase chain reaction (PCR) provides evidence of active HCV infection and is potentially useful for confirming the diagnosis and monitoring the antiviral response to therapy. Optimal HCV PCR assays at present have a sensitivity of less than 100 copies of HCV RNA per millilitre of plasma or serum. Molecular tests have also been developed to classify HCV into distinct genotypes;
- *Diagnostic tests for the detection of HBV infection:*

  I - Serological assays for HBV serological markers (HBsAg, anti-HBs Ac, anti-HBc Ac, HBeAg, anti HBe Ac) by Enzyme-linked immunosorbent Assay (ELISA)

  II - Molecular tests to detect viral particles. Testing for HBV DNA (PCR) to confirm the diagnosis and quantify the number of viral copies in the blood (viremia).

- Histological assessment: liver histopathological examination (performed on liver fragment obtained from liver biopsy, liver transparieto) with the separate evaluation of necroinflamatorylesions and liver fibrosis using Knodell score .

Statistical analysis:

For storing the information registered on the plug of study in a database and also for statistical calculations we used statistical software MedCalc ® version 12.5.0.0 Medical (MedCalc ® Software, Broekstraat 52, 9030 Mariakerke, Belgium), Windows XP / Vista / 7/8 .. Statistical test results will be represented by probability hypothesis "null" (p), its value below 0.05 shows a statistically significant difference between the groups studied.

Statistical analysis was performed according to the protocol of a randomized clinical trial on 2 groups of patients comparable age, sex, etiology of disease, laboratory parameters, histological parameters.

RESULTS AND DISCUSSION

We conducted a descriptive research of group 1 - patients with HCV, group which included 210 patients of which 101 women with a mean age of 42.7 years, mean weight 68.5 kg and an average height of 1.69m, 109 men with a mean age of 43.4 years, mean weight 70.2 kg and an average height of 1.70m I have studied body mass index at women who ranged between 22.63 and 24.97 with a mean of 23.80, a minim of 14.69 and a maximum of 43.38 and between 23.26 and 25.27 in men with an average of 24.27, a minimum of 15.02 and a maximum of 43.38. Analyzing the fasting glucose I observed an average 99.82 mg/dl at females and 96.57 md/dl at males. Alanine aminotransferase (ALT) had average values of 116.7 U/L at women and 124, 5 U/L at men. Viral load, important in the response to treatment we analyzed in our group of patients finding at women mean viral load 3578702 UI/L and at men 4020733 UI/L.

Table 1. The synoptic characterization of group1

	Women				Men			
	N	Mean(95%CI)	Min.	Max.	N	Mean (95%CI)	Min.	Max.
Age (year)	101	42.7 (40.4 - 45.0)	19	64	109	43.4 (41.2 - 45.6)	19	64
Weight (kg)	101	68.05 (64.79 - 71.32)	43	121	109	70.21 (67.56 - 72.85)	41	124
Height (m)	101	1.69 (1.67 - 1.71)	1.55	1.91	109	1.70 (1.68 - 1.72)	1.55	1.94
BMI (kg/m2)	101	23.80 (22.63 - 24.97)	14.69	43.38	109	24.27 (23.26 - 25.27)	15.02	43.38
Glycemia (mg/dl)	101	99.82 (96.82 - 102.82)	66.00	125.00	109	96.57 (93.47 - 99.68)	55.00	119.00
HCV-RNA (UI/ml)	101	3578702 (296794 - 4189464)	130000	15600000	109	4020733 (3402978 – 4638489)	99000	13600000
ALT (U/L)	101	116,7 (104,4 - 129,0)	31	231	109	124,5 (113,7- 135,3)	32	231

We also performed a research related to the influence of clinical and biochemical and histological parameters. These parameters were included in an analysis of AUC (area under curve) in order to estimate their degree of influence on getting SVR. The results are shown in the table below.

Tabel 1.The interpretation of the lot trough AUC analysis

	AUC	**Eroare std.**	**95% CI**	**Predictive value**
HOMA_IR	0,863	0,0353	0,794 - 0,932	YES
Initial value HCV RNA	0,822	0,0342	0,755 - 0,889	YES
Fasting insulin	0,803	0,0434	0,718 - 0,888	YES
Fastin glucose	0,772	0,0409	0,691 - 0,852	YES
*d_VL_*	0,686	0,0461	0,595 - 0,776	YES
BMI	0,573	0,0538	0,467 - 0,678	NO
AST	0,564	0,0545	0,457 - 0,671	NO
Serum ferritin	0,526	0,0536	0,421 - 0,631	NO
Serum Triglyceride	0,518	0,0564	0,407 - 0,628	NO
Weight	0,518	0,0564	0,407 - 0,628	NO
Age	0,517	0,0541	0,411 - 0,623	NO
Serum cholesterol	0,511	0,0560	0,402 - 0,621	NO
ALT	0,508	0,0551	0,400 - 0,616	NO

Tabel2.The interpretation of histological parameters trough AUC analysis

	AUC	**Eroare std.**	**95% CI**	**Predictive value**
Liver iron score	0,873	0,0307	0,813 to 0,934	YES
Fibrosis score (ISHAK)	0,849	0,0413	0,768 to 0,930	YES
Steatosis score	0,682	0,0532	0,577 to 0,786	YES
Necroinflammatoryscore (HAI)	0,549	0,0525	0,446 to 0,651	NO

Based on the obtained results, it appears that only the values of HOMA index, those of insulinemia values, alongside initial value of HCV RNA, dVL parameter value (low relative percentage of viral load during the first 12 weeks of treatment), mean blood glucose values at baseline, as well as values of histological scores of fibrosis (Ishak), steatosis and hepatic iron loading, may be predictive in the early viral response in chronic hepatitis C.

A descriptive research we conducted also in the case of group 2 - patients with chronic hepatitis B that included 166 patients of which 72 women with a mean age of 44.3 years, mean weight 66.9 kg, 94 men with a mean age of 45.3 years, mean weight 70.7 kg. I have studied body mass index at women who ranged between 22.5 and 25.1 with a mean of 23 and males between 23.3 and 25.6 with a mean of 24.5. Among the biochemical analysed parameters glycaemia also is included, aiming its fasting value. We followed fasting glucose values and found an average of 99.82 mg/dl in women, 98.0 mg/dl in men. We followed fasting glucose values and found an average of 99.82 mg/dl at women, 98.0 mg/dl at men. Was dosed alanine aminotransferase (ALT) resulting average values for the woman 154 U/L and for the men 143.1 U/L and aspartate aminotransferase (AST) in women with mean values of 135 U/L for men and 119 U/L.Viremia, important on the response to treatment, we analyzed it in our group of patients finding for women a mean viral load 3425458UI/L and for the men 3681361 UI/L.

Tabel 64. The synoptic characterization of group2

	Women			Men		
	N	Mean	95% CI	N	Mean	95% CI
Age(year)	72	44,361	41,369 - 47,354	94	45,372	42,919 - 47,825
Fastin glucose(mg/dl)	72	101,653	98,108 - 105,197	94	98,074	94,427 - 101,722
Fasting insulin (µU/mL)	72	13,231	12,071 - 14,390	94	11,867	11,008 - 12,726
weight (kg)	72	66,972	63,603 - 70,341	94	70,798	67,855 - 73,741
BMI (kg/m2)	72	23	22,502 - 25,161	94	24,515	23,396 - 25,635
ALT T0 (U/L)	72	154	136,654 - 172,512	94	143,138	129,039 - 157,238
AST T0 (U/L)	72	135	118,986 - 152,847	94	119,085	105,924 - 132,246
HBV DNA T0 (UI/ml)	72	3425458	2692369 - 4158547	94	3681361	2984874 - 4377848

As in patients with chronic hepatitis C, in the case of patients with chronic hepatitis B, the researched parameters were included in an analysis type AUC (area under curve) in order to estimate their degree of influence on the viral response after 6 months. The results are shown in the table below.

Tabel 4.The interpretation of the lot trough AUC analysis

	AUC	St.error	95% CI	Predictive value
HOMA_IR	0,724	0,0428	0,640 to 0,808	YES
Initial value of HBV-DNA	0,721	0,0397	0,643 to 0,799	YES
Fasting insulin	0,694	0,0426	0,610 to 0,777	YES
Fasting glucose	0,638	0,0440	0,552 to 0,725	YES
Weight	0,603	0,0484	0,508 to 0,697	NO
Serum cholesterol	0,597	0,0474	0,504 to 0,690	NO
BMI	0,574	0,0488	0,478 to 0,670	NO
Serum ferritin	0,557	0,0480	0,463 to 0,651	NO
Age	0,528	0,0480	0,434 to 0,622	NO
AST	0,521	0,0498	0,423 to 0,619	NO
Serum Triglyceride	0,514	0,0499	0,416 to 0,611	NO
ALT	0,504	0,0498	0,406 to 0,601	NO

Tabel 6. The interpretation of histological parameters trough AUC analysis

	AUC	St.error	95% CI	Predictive value
Fibrosis score (ISHAK)	0,754	0,0389	0,677 to 0,830	YES
Liver iron score	0,663	0,0473	0,571 to 0,756	YES
Necroinflammatory score (HAI)	0,549	0,0492	0,453 to 0,646	NO
Steatosis score	0,523	0,0464	0,432 to 0,614	NO

From the overall analysis of the above results, it appears that only HOMA index values, that of fasting insulin, together with baseline HBV DNA, ALT values, mean blood glucose at the beginning of treatment, and also values of the histological fibrosis score (Ishak) and liver iron score, may be predictive of the early viral response in chronic hepatitis B.

In brief, our research proves that the factors involved in the treatment failure related to the chronic hepatitis c are linked to older age, high viral load, and impaired glucose tolerance at the beginning of the treatment (high fasting glucose and insulin, high HOMA index) and also to liver histology features (high fibrosis score, liver steatosis, iron infiltration, and more or less high necroinflammatory activity). Indeed, while those factors were also observed at least in part by other authors, some controversies still exists regarding punctual aspects.I noticed that all the parameters that define insulin resistance (elevated fasting glucose, elevated fasting insulin and increased HOMA index) are negative predictors for achieving both EVR and SVR.

Evaluation of potential parameters that may have a predictive value for the development of chronic hepatitis B showed that there are a number of factors that can interfere with the viral response. Viral load, fibrosis score, liver iron score and insulin resistance index seem to have a significant degree of predictability in terms of viral response to therapy in chronic hepatitis B. Indeed, patients with high fibrosis score, high viral load and high degree of insulin resistance were less likely to achieve a virological response in chronic hepatitis B treated with Peg IFN, regardless of age, BMI, hepatic cytolysis enzymes, cholesterol and triglycerides.

CONCLUSIONS

This research included 376 patients diagnosed with chronic hepatitis B and C, divided into 2 groups, which I analyzed the influence of steatosis and conjugates factors on the response to antiviral therapy.

We performed a descriptive statistics of the groups studied for a better understanding of the clinical profile of patients and for the initiation of optimal therapies.

Factors connected totreatment failure were: older age, high viral load, insulin resistance and liver histological features such as steatosis, fibrosis score, iron infiltrationscore and more or less necroinflamatory activity score.

1. *We found that older age has a negative correlation with viral response. Around the age of 50 already EVR rate decreases to 50%. The average age of patients in the study group with chronic hepatitisC was 43.1 years and in the group with chronic hepatitis B, 44.9 years.*
2. *The high viral load is a strongly negative predictor for therapeutic success.. The low pre-treatment level of HCV RNA was statistically significantly correlated with virologic response in patients with chronic hepatitis C treated with α-IFN and ribavirin.*
3. *We noticed no influence related to the degree of cytolysis or to serum ferritin levels, not having predictive value on achieving EVR.*
4. *Our research demonstrates that all the parameters defining insulin resistance (high fasting glucose, high fasting insulin, and high HOMA index) are negative predictors for achieving both EVR and SVR.*
5. *The patients with chronic hepatitis C and low pre-treatment level of HCV RNA, without steatosis and normal BMI were statistically significantly correlated with achieving a sustained virological response.*
6. *Our research demonstrates that a high degree of liver steatosis impairs both EVR and SVR in genotype 1 chronic hepatitis C treated with standard PegIFN and*

ribavirin for 48 weeks and that a steatosis score of ≤3 predicts EVR with a sensibility of 91.03% and a specificity of 21.54%.

7. *Analyzing the results of our study shows that HOMA-IR index , the serum insulin levels, baseline HCV RNA, baseline mean blood glucose and histological scorelike fibrosis score (Ishak), steatosis score and liver iron score may have a predictive value for obtaining an early viral response in chronic hepatitis C.*
8. *In our opinion, liver iron score is an important predictor for both EVR and SVR. Our research demonstrates that an iron score of less than 27 can predict a favourable therapeutic effect with a sensibility of 97.93% and a specificity of 21.54%.*
9. *The index HOMA, serum insulin levels alongside baseline DNA HBV levels, baseline mean blood glucose and histological score like fibrosis score (Ishak), steatosis score and liver iron score may have a predictive value for obtaining an early viral response in chronic hepatitis B.*
10. *The predictive factors of a favourable response to patients with chronic hepatitis B treated with α- IFN are represented by younger age, serum levels of ALT and HBV DNA levels.*
11. *Patients with high fibrosis score, high viral load and high degree of insulin resistance were less likely to acquire a virological response in chronic hepatitis B treated with Peg-IFN, regardless of age, BMI, hepatic cytolysis enzymes, cholesterol and triglycerides.*
12. *There are a number of factors which can interfere with the viral response. Viral load, fibrosis score, liver iron score and insulin resistance index seem to have a significant degree of predictability with regard to viral response to the treatment in chronic hepatitis B. Thus, patients with high fibrosis score, high viral load and high degree of insulin resistance were less likely to acquire a virological response in chronic hepatitis B treated with Peg-IFN, regardless of age, BMI, hepatic cytolysis enzymes, cholesterol and triglycerides.*
13. *Some authors suggested a "protective" effect of steatosis in patients with chronic hepatitis B, based on clinical and experimental data but also there are studies that deny any interference between steatosis and viral response, considering that liver steatosis is only a relatively common finding in chronic hepatitis B and metabolic*

host factors rather than viral factors are responsible for the presence of steatosis in these patients.

As for steatosis, in our opinion it seems that it has no role in predicting viral response, and that it is only a factor that coexists more or less with histologic changes of the liver in chronic hepatitis B, somewhat like an "innocent bystander". Little is known about the steatosis in chronic hepatitis B, and various groups emphasized conflicting conclusions regarding this aspects, ranging from a presumptive "protective effect" of steatosis in the outcome of treatment in patients with chronic hepatitis B, to "no effect at all" or to a "deleterious effect" like in the case of chronic hepatitis C.

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