

ANALYSIS OF THE SUSTAINED VIROLOGICAL RESPONSE IN PATIENTS WITH CHRONIC HEPATITIS C AND LIVER STEATOSIS

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ABSTRACT – *Context* - Chronic hepatitis C as well as non-alcoholic fatty liver disease are recognized as the main cause of liver disease in Western countries. It is common to see the concomitance of the diseases and the influence of steatosis in the sustained virological response of patients with hepatitis C virus. *Objective* - Assess the sustained virological response in chronic hepatitis C patients according to the presence of liver steatosis. *Methods* - One hundred sixty patients with chronic hepatitis C were retrospectively evaluated. Demographic data such as gender, age, body mass index, presence of diabetes mellitus and systemic arterial hypertension, virus genotype and use of pegylated interferon were analyzed, as was the staging of fibrosis and the presence of steatosis at histology. *Results* - Most patients were male (57.5%), with a mean age of 48 ± 9.7 years. The most frequent genotype observed was 3 (56.9%) and, in the histological evaluation, steatosis was observed in 65% of the patients (104/160). Sustained virological response in patients with steatosis occurred in 38.5%, and in 32.1% in patients without steatosis ($P = 0.54$). When we analyzed possible factors associated with the presence of steatosis, only body mass index and systemic arterial hypertension revealed a significant association. When the factors that influenced sustained virological response were evaluated in a logistic regression, genotype and use of pegylated interferon proved to be independent factors associated to the response. *Conclusion* - In the evaluated patients the presence of liver steatosis did not influence the sustained virological response of patients with chronic hepatitis C treated with interferon and ribavirin.

HEADINGS - Hepatitis C, chronic. Fatty liver. Antiviral agents.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a pathological clinical syndrome that ranges from isolated liver steatosis to non-alcoholic steatohepatitis (NASH), which can progress to advanced fibrosis and cirrhosis⁽⁷⁾. Estimates based on imaging studies and autopsies suggest that approximately 20%-30% of American adults and those from Western countries have an accumulation of liver fat^(3, 6, 7, 15, 46), and approximately 10% of these individuals have NASH. This is frequently associated with adult age, female gender, obesity, diabetes mellitus (DM) type 2, hypertriglyceridemia, dyslipidemia and other conditions characterized by resistance to insulin and hyperinsulinemia^(7, 11, 52). A study conducted by our group⁽⁶⁰⁾ demonstrated that NASH is also a common disease among obese, non-diabetic patients, with altered levels of aminotransferases, occurring in 3.18% and,

as a rule, presenting itself as a mild disease, although more intense cases may also be observed.

Liver steatosis is one of the most frequent histological findings in chronic hepatitis C (CHC) patients, observed in approximately 55% of those patients^(1, 8, 14, 19, 26, 28, 29, 37, 40, 42, 43, 45, 49, 59). In a recent study, Coral et al.⁽¹⁷⁾ revealed steatosis in 55 % of the patients infected by hepatitis C virus (HCV), correlating with genotype 3, but not with the degree of liver fibrosis.

The mechanisms through which the HCV causes liver damage associated with steatosis are poorly understood. It seems that the accumulation of fat in the hepatocytes of patients with CHC occurs mainly due to an effect of the virus itself strengthened by metabolic factors related to the host^(19, 42, 50, 53). The virus interferes with genes expression increasing de novo fatty acids synthesis and decreasing both hepatocyte lipids export and fatty acids consumption (oxidation). It seems that HCV increases the production of TNF (tumor

Study conducted at the Gastroenterology and Hepatology Unit of Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSA), Porto Alegre, RS, Brasil.
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necrosis factor), leading to insulin resistance: TNF probably affects insulin receptor substrate (IRS-1) phosphorylation, decreasing glucose captivation and promoting compensatory hyperinsulinemia. Besides this, it is possible that liver siderosis and alterations in the levels of circulating adipocytokines might as well have a role in insulin sensitivity in CHC⁽³⁹⁾. Nevertheless, Mello et al.⁽³⁵⁾ failed to find an enhancement in insulin resistance, evaluated by HOMA (homeostatic model assessment), with the treatment of HCV.

There is agreement among several authors that the physiopathology of liver steatosis associated with HCV is different in patients infected by genotype 1 or 3^(4, 12, 23, 31, 47, 49). Thus, the association between CHC and steatosis in patients infected by HCV genotype non-3, especially in those with genotype 1, seems to be related to pre-existing factors of the host, and is called “metabolic steatosis”. In this group of patients, the intensity of fat accumulation is proportional to BMI and the degree of visceral obesity, and there is no improvement after negativation of the virus through antiviral treatment^(13, 33). On the other hand, in patients with HCV genotype 3, steatosis is related to higher viral loads and usually decreases after HVC treatment; this virus probably leads to hypobetalipoproteinemia, affecting liver release of triglycerides in bloodstream as VLDL (very low density lipoprotein)⁽³⁹⁾.

The presence and intensity of liver steatosis is considered a marker of liver disease progression in patients with CHC, and it also seems to have an impact on sustained virological response (SVR) in these patients when submitted to antiviral therapy^(48, 53). It is possible that hyperinsulinemia could block the inhibition of HCV replication by interferon, since insulin and interferon share signal transduction factors, such as p38 MAP kinase; PI3 kinase and IRF-1 also might be associated^(18, 39).

The main objective of this study was to assess SVR in patients with CHC and to relate it to the presence of hepatic steatosis.

METHODS

This is a retrospective study in which medical records of patients with CHC were assessed after they had undergone liver biopsy between January 2001 and December 2006, at Hospital Irmandade Santa Casa de Misericórdia de Porto Alegre, RS, Brasil.

The criteria for inclusion were: be over the age of 18, be infected by HCV, have undergone a liver biopsy, have concluded treatment with conventional or pegylated interferon associated with ribavirin at least 6 months prior to data collection with the intent of evaluating sustained virological response. Currently, in Brazil, the Public Health System provides treatment for naïve CHC patients with pegylated interferon if HCV genotype-1 and with conventional interferon if other genotypes of HCV.

In order to avoid possible confusion factors, daily alcohol consumption of more than or equal to 40 g/day for men and 20 g/day for women and other causes of liver disease such

as infection by hepatitis B virus, auto-immune hepatitis, hemochromatosis, Wilson’s disease, alpha 1-antitrypsin deficiency and use of hepatotoxic medications were considered criteria for exclusion. Patients with decompensated liver disease, patients infected with HIV, patients with renal insufficiency and patients with any sort of neoplasia were also excluded. Other criteria for exclusion were liver biopsies with histological representation of less than seven portal spaces and incomplete medical records.

All patients had their diagnosis of HCV infection confirmed by PCR⁽⁵⁶⁾ and genotyping was conducted by restriction fragment length polymorphism technique⁽⁵⁵⁾.

Age, gender, body mass index (BMI – using the weight/height² formula)⁽¹⁶⁾, presence of DM (defined as fasting glycemia greater than or equal to 126 mg/dL in at least two measurements)⁽⁵⁾, presence of SAH – systemic arterial hypertension (defined as systolic blood pressure - BPs – greater than or equal to 140 mm Hg or diastolic blood pressure - Bpd – greater than or equal to 90 mm Hg)⁽⁵¹⁾ and the serum levels of the following exams were evaluated: aminotransferases, total cholesterol, HDL (high density lipoproteins), triglycerides and γ -GT.

With regard to BMI, it was considered normal a BMI less than or equal to 25 kg/m²; overweight, BMI between 25.1 and 29.9 kg/m²; and obesity, BMI greater than or equal to 30 kg/m². Two groups were considered for statistical analysis: BMI \leq 25 kg/m² and BMI >25 kg/m².

The type of treatment conducted, interferon α and ribavirin or pegylated interferon and ribavirin, was also considered. In order to analyze response to treatment, two groups were considered: those who achieved SVR when the qualitative RNA-HCV was negative in the 6th month after conclusion of treatment and the non-responders, patients who did not have a 2 log drop in quantitative RNA-HCV in week 12, patients who did not negativate qualitative RNA-HCV at the end of treatment or who had a positive qualitative RNA-HCV in the 6th month after conclusion of the same (recurrents).

Liver fragments obtained in liver biopsies were colored with H-E, picosirius and Prussian blue dyes to assess steatosis and inflammatory activity, liver fibrosis and iron load, respectively.

The Metavir⁽³⁰⁾ classification was used for chronic hepatitis C and the Brunt⁽¹¹⁾ classification for NAFLD. For statistical analysis, the patients were divided into two groups according to degree of fibrosis: absence of fibrosis to moderate fibrosis (F0-F1-F2) and intense fibrosis (F3-F4).

NASH was defined according to the American Association for the Study of Liver Diseases classification⁽¹¹⁾.

All biopsies were reviewed by a single pathologist who did not know the patients’ clinical and laboratory data.

The study was submitted to and approved by the Ethics Committee of the Hospital Irmandade Santa Casa de Misericórdia de Porto Alegre.

Age, weight, height and body mass index were analyzed as means and standard deviation. Laboratory exams such as serum glycemia, aminotransferases and γ -GT were also calculated as means and standard deviation. The sustained

virological response was calculated by frequency and percent, generating an SVR rate. Other categorical variables were also expressed in frequency and percent. The association of the variables and SVR was evaluated by OR - odds ratio, with a 95% confidence interval. Chi-square or Fisher's exact test were used when necessary. Potential confusion effects were removed in a logistics regression model and a 5% index of significance was adopted ($\alpha = 0.05$). The statistical analysis was done using the SPSS 12.0 package.

RESULTS

Of a total of 396 patients with CHC, 120 did not meet the criteria for inclusion: 24 for being in treatment during the data collection period; 2 because they suspended treatment before completing it due to intolerance; 28 for being HIV-positive; 11 for having concomitant hepatitis B virus; 4 for undergoing lung and kidney transplants during the study period; 8 for having several types of neoplasia (including a case of hepatocellular carcinoma); 3 patients with decompensated cirrhosis; 4 alcohol abusing patients; 18 patients with chronic renal insufficiency who were undergoing treatment with interferon in monotherapy; and 18 patients with chronic renal insufficiency whose liver biopsy was considered insufficient.

Ninety-six patients were also excluded from the protocol for not having any indication of treatment during this period and 20 patients for incomplete data because they had missed follow-ups at the clinic.

Thus, 160 patients met the previously established criteria of inclusion and were evaluated for this study.

The majority of patients was male (92/160 - 57.7%) and mean age was 48 years, with a standard deviation of 9.7. The mean weight of the patients was 73.66 kg, with a standard deviation of 13.58 kg. Mean height was 1.68 m, with a standard deviation of 0.09 m. Mean body weight index was 26.07 kg/m², with a standard deviation of 4.5 kg/m². These data and those that refer to the laboratory exams can be appreciated in Table 1.

TABLE 1. Demographic characteristics and laboratory data of evaluated patients

Characteristics	Mean	Standard deviation
Age (years)	48	9.7
Weight (kg)	73.66	13.58
Height (m)	1.68	0.09
BMI (kg/m ²)	26.07	4.5
Fasting glycemia (mg/dL)	96.74	26.04
ALT (mg/dL)	111.94	94.61
AST (mg/dL)	76.86	56.96
γ -GT (mg/dL)	93.32	124.97
Total cholesterol (mg/dL)	163.27	39.33
HDL cholesterol (mg/dL)	45.35	12.1
Triglycerides (mg/dL)	109.85	48.79

BMI = body mass index

Of the 160 patients studied, genotype 3 was the most prevalent, being found in 91 patients (56.9%), while genotype 1 was found in 60 patients (37.5%), and genotype 2, in 9 patients (5.6%).

In the analysis of liver biopsy, grade 0 fibrosis was found in 3 patients (1.9%); grade 1 fibrosis, in 31 (19.4%); grade 2 fibrosis, in 68 patients (42.5%); grade 3 fibrosis, in 34 (21.3%); and grade 4 fibrosis, in 24 (15%). Most patients (102 - 63.8%) belonged to the absent fibrosis to moderate fibrosis group.

Analyzing the degree of steatosis found in liver biopsies, steatosis was observed to be present in 104/160 patients (65%). Among these, 76 (47.5%) presented steatosis in less than 33% of the hepatocytes, that is, grade 1 steatosis; 21 patients (13.1%) had between 33% and 66% of the hepatocytes with steatosis, that is, grade 2; and 7 patients (4.4%) presented more than 66% of their hepatocytes with steatosis, characterizing grade 3 steatosis. Among the patients with steatosis, in 98/104, it was macrovesicular, which represents 94.2%. Mixed steatosis was observed in 6/104, representing 5.8% of the sample.

The presence of NASH was only observed in eight patients studied (5%) and, for that reason, this data was not submitted to statistical analysis.

Among patients with genotype 3, steatosis was observed in 64/91 patients (61.5%). In the other genotypes, the presence of steatosis was observed in 40/69 (38.5%) patients.

DM was found in 19 patients, which represents 11.9% of the sample studied. Twenty-four patients (15%) were diagnosed with arterial hypertension.

When the antiviral treatment used by the patients was analyzed, only 48 (30%) patients had undergone treatment with pegylated interferon associated with ribavirin. Conventional interferon associated with ribavirin was the treatment of choice for 70% of the patients (112/160).

In analysis of the virological response, SVR was found in 58 patients, representing 36.3% of the sample, while non-responders represented 73 patients (45.6%), and recurrences, 29 patients (18.1%).

The results found, in accordance with group characteristics, taking into account the presence of steatosis, are shown in Table 2.

TABLE 2. Characteristics analyzed in relation to the presence of steatosis

Characteristics	Steatosis n = 104 (65%)	Without steatosis n = 56 (35%)	P
Age >40 years	89 (85.6%)	41 (73.2%)	0.09
BMI >25 kg/m ²	65 (62.5%)	18 (32.1%)	<0.01
Genotype			0.08
1	37 (35.6%)	23 (41.1%)	
2	3 (2.9%)	6 (10.7%)	
3	64 (61.5%)	27 (48.2%)	
Fibrosis			0.45
0.1 and 2	69 (66.3%)	33 (58.9%)	
3 and 4	35 (33.7%)	23 (41.1%)	
Diabetes	11 (10.6%)	8 (14.3%)	0.66
SAH	22 (21.2%)	2 (3.6%)	0.01

BMI = body mass index

SAH = systemic arterial hypertension

TABLE 3. Evaluated factors and their relation with sustained virological response

Characteristics	n	SVR	Logistic regression		
			OR	CI95%	P
Steatosis					
Yes	104	40 (38.5%)	1.5	0.7 to 3.4	0.29
No	56	18 (32.1%)			
Age					
≥40	130	41 (31.5%)	0.3	0.1 to 0.8	0.33
<40	30	17 (56.7%)			
BMI					
≥25	83	30 (31.5%)	0.8	0.4 to 1.6	0.50
<25	77	28 (36.4%)			
Genotype					
1	60	17 (28.3%)	6.1	1.6 to 22.7	<0.01
2 and 3	100	41 (41.0%)			
Fibrosis					
0, 1 and 2	102	40 (39.2%)	0.7	0.3 to 1.4	0.26
3 and 4	58	18 (31.0%)			
Peg-interferon use					
Yes	48	20 (41.7%)	7.2	1.9 to 22.4	<0.01
No	112	38 (33.9%)			

SVR = sustained virological response

OR = odds ratio

CI = confidence interval

Analyzing liver steatosis and its relation to SVR, it was observed that from 104 patients who had liver steatosis in the biopsy, 40 (38.5%) had SVR, whereas in the group of patients without steatosis this number was 18/56 (32.1%), with no statistical difference. These data and those that refer to the relation between SVR and age, BMI, genotype, grade of fibrosis and type of interferon used can be analyzed in Table 3.

This study revealed that, in genotype 1, the presence of steatosis was associated with SVR in 14/37 (11.2%) versus 2/23 (2.98%) without steatosis ($P = 0.06$). In patients with genotypes 2 and 3 who achieved SVR, steatosis was present in 33% (26/67) versus 34.2% (15/33) of those without steatosis ($P = 0.99$).

DISCUSSION

There is a study that suggests that steatosis can induce a mechanism of resistance to antiviral therapy⁽⁴²⁾. This mechanism is still unknown, but it seems to be independent of other known response factors, such as genotype 1, high viral load and extensive fibrosis as well as metabolic factors. This mechanism also seems to be specific of the so-called “metabolic steatosis”, since the “viral steatosis” observed in genotype 3 is not associated with a low rate of sustained virological response.

The negative effect of steatosis on the response to antiviral treatment may be caused by the reduction in bioavailability of antiviral drugs and/or host factors, such as more advanced disease and/or coexistence of other associated diseases⁽⁵⁵⁾. Another possible explanation for steatosis' interference in the

response to antiviral treatment is associated with resistance to insulin, considering the “two stage” hypothesis suggested by Day et al.⁽²⁰⁾, in 1998. It is possible that hyperinsulinemia blocks inhibition of HCV mediated by interferon, by interacting with interferon's regulator factor, impeding its activation⁽³¹⁾.

Liver steatosis is present in around 55% of patients infected by HCV, varying between 40% and 86% of the cases^(36, 43). In the present casuistics, steatosis occurred in 65% of the patients, which is in agreement with the data found in literature⁽⁴²⁾.

In a general sense, steatosis present in patients infected by HCV is grade 1, affecting less than 33% of the hepatocytes^(8, 12, 17, 45), which was also found in this study (47.5% of the biopsies).

This study did not show any significant association between age and the presence of steatosis, but did with BMI, which was also shown by other authors^(25, 26, 27, 29, 37, 42, 47, 52).

There is a tendency to associate the hepatitis C genotype 3 virus with the presence of steatosis^(2, 8, 12, 28, 36, 37, 40, 42, 43, 45, 48, 57), also found in this study, in which 61.5% of HCV genotype 3 patients had steatosis in the biopsy. The presence of steatosis was observed in fewer patients with genotypes other than 3. However, despite the higher prevalence of steatosis in genotype 3, there was no statistical difference among groups. Unfortunately, it was not possible to evaluate the existence of a relation between HCV genotype 3 viral load and steatosis, since Brazilian Public Health System does not provide viral load measurements for this genotype.

Some authors^(1, 36, 43), when seeing an association between liver steatosis and genotype 3, suggested that a specific viral sequence of this genotype could be responsible for this “steatotic phenotype”. It must be pointed out that improvement in steatosis

is associated with the negatization of the HCV genome in the hepatocyte.

Rubbia-Brandt et al.⁽⁴⁴⁾ confirmed, in a multivariate analysis, that the association between the presence and severity of liver steatosis in patients infected by genotype 3 is not fortuitous, since HCV genotype 3 patients had a tenfold greater chance of presenting liver steatosis in biopsy, regardless of other factors such as alcohol use, overweight/obesity and use of injectable drugs.

With regard to the relationship between steatosis and liver fibrosis, several studies have demonstrated a positive association^(19, 26, 29). Studies that evaluated sequential liver biopsies proved this association^(12, 22, 57). Thus steatosis has been considered a co-factor for liver fibrosis. In the casuistics under study, and as referred by other authors^(8, 32), an association was not demonstrated between the presence of steatosis and fibrosis.

The relationship between the metabolic syndrome and the presence of liver steatosis is well-known. Furthermore, common findings of this syndrome, such as obesity, diabetes, arterial hypertension and hypertriglyceridemia, are strongly associated with the presence of NAFLD in CHC patients⁽⁴⁷⁾.

In our study, the presence of DM was only observed in 19 patients, without any relationship between this finding and the presence of steatosis. This fact is believed to result from the small number of cases with diabetes. However, it was possible to demonstrate that the presence of systemic arterial hypertension was related to the finding of liver steatosis.

In this study, 36.3% of the patients achieved SVR, which is in agreement with the values found in a previous study conducted by our group⁽²¹⁾.

In relation to SVR, of the diverse parameters evaluated, only genotype and pegylated interferon use in antiviral treatment achieved statistical significance in a multivariate analysis. BMI, age, fibrosis and steatosis did not correlate with SVR in this analysis.

The mechanisms through which obesity can affect response to antiviral treatment are not totally understood. BMI has been related to the degree of steatosis observed in chronic hepatitis C^(10, 26). Bressler et al.⁽¹⁰⁾ demonstrated that obesity, defined as BMI > 30 kg/m², is a risk factor for non-response to antiviral treatment, regardless of genotype and the presence of liver cirrhosis. In this study, BMI was not associated with SVR, as in other studies^(40, 42).

Most of the patients in this study were over 40 years of age, which could probably be one of the factors to explain the

population's low SVR. In younger patients, SVR was found in 56.7% corroborating the fact that age is related to response to treatment in patients infected by HCV^(9, 24, 33, 34, 40, 61). However, it must be underscored that no association was found between age and SVR in this study.

When analyzing liver fibrosis, no statistically significant correlation was found between the grade of fibrosis and SVR, although patients with lower grades of fibrosis obtained a better SVR^(38, 41).

In the casuistics in question, the presence of steatosis did not exert any influence on SVR, different from what was found in other studies^(40, 42). It is possible that it could relate to a type-II error, since our study has a smaller sample than others, but, recently, it has been published some data corroborating our findings. Cross et al.⁽¹⁸⁾, for instance, found that only HCV genotype and pretreatment weight were associated to SVR in a multivariate analysis; neither steatosis, nor steatohepatitis were considered independently associated with this outcome. It is possible, then, that pretreatment weight and not steatosis would affect the treatment results; nevertheless, we did not find association between BMI and SVR either.

As in literature^(24, 31, 34, 42, 53), in a multivariate analysis, this study demonstrated that patients with HCV genotypes 2 and 3 had a better SVR rate when compared to those with genotype 1.

Westin et al.⁽⁵⁸⁾, in a European multicentric study, demonstrated that 88% of the genotype 3 patients obtained SVR, regardless of the high prevalence of steatosis and pretreatment viral load found in this group. In genotypes other than 3, a 56% SVR rate was found, and, in patients with steatosis, this rate was of 46%, whereas, in those without steatosis this rate was of 65%, demonstrating the impact of steatosis on SVR in these patients. This group suggests that weight loss should be the objective of an intervention in the patients' life habits with the intent of creating better conditions for antiviral therapy success.

The improvement in SVR rate has been demonstrated by several authors when the antiviral treatment of choice is pegylated interferon associated with ribavirin^(24, 34, 38, 61). This study did not present any different results, despite the small number of patients treated with pegylated interferon. When a logistics regression analysis was made, a statistically significant association was found between type of interferon used and SVR.

In conclusion, steatosis did not seem to influence SVR in our group of patients treated for CHC with interferon and ribavirin.

Piccoli LZ, Mattos AA, Coral GP, Mattos AZ, Santos DE. Análise da resposta virológica sustentada em pacientes com hepatite crônica pelo vírus da hepatite C e esteatose hepática. *Arq Gastroenterol.* 2011;48(3):179-85.

RESUMO – Contexto - Tanto a hepatite crônica pelo vírus C quanto a doença hepática gordurosa não-alcoólica são reconhecidas como causas frequentes de doença hepática nos países ocidentais. É comum observar a concomitância das duas doenças e a influência da esteatose na resposta virológica sustentada dos pacientes com hepatite crônica pelo vírus C. **Objetivo** - Avaliar a resposta virológica sustentada nos pacientes com hepatite crônica pelo vírus C de acordo com a presença de esteatose. **Métodos** - Foram avaliados, retrospectivamente, 160 pacientes com hepatite crônica C. Dados demográficos, como sexo, idade, índice de massa corpórea, presença de diabetes mellitus e hipertensão arterial sistêmica, genótipo do vírus e uso de interferon peguilado foram analisados, bem como o estadiamento e a presença de esteatose, quando da histologia. **Resultados** - A maioria dos pacientes era masculina (57,5%), com média de idade de 48 anos ± 9,7. O genótipo mais frequente foi o 3 (56,9%) e, na avaliação histológica, foi observada esteatose em 65% dos pacientes (104/160). A resposta virológica sustentada nos pacientes com esteatose foi de 38,5%, sendo de 32,1% nos pacientes sem esteatose ($P = 0,54$). Quando se analisaram possíveis fatores associados à presença de esteatose, somente índice de massa corpórea e hipertensão arterial sistêmica estiveram associados de forma significativa. Quando se avaliaram em regressão logística os fatores que influenciaram a resposta virológica sustentada, genótipo e uso de interferon peguilado mostraram-se fatores independentes associados à resposta. **Conclusão** - A presença de esteatose hepática não influenciou a resposta virológica sustentada de pacientes com hepatite crônica pelo vírus C tratados com interferon e ribavirina.

DESCRIPTORIOS - Hepatite C crônica. Fígado gorduroso. Antivirais.

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