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STATINS – A NEW OPTION FOR THE ANTIVIRAL TREATMENT? PRELIMINARY STUDY

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Abstract: *Statins, which are typically used as anti-cholesterol medication, can inhibit the replication of the hepatitis C virus. The anti-HCV activity is not related with cytotoxicity; they inhibit the replication of HCV RNA via inhibition of HMG-CoA reductase which leads to reduction of intracellular mevalonate and consequently to reduction of geranyl-geranyl pyrophosphate. HCV RNA replication needs some geranyl-geranylated proteins which need the geranyl-geranyl pyrophosphate of the host cell. The objective of this prospective study was to sustain the antiviral effect of statins.*

Key words: *Statins, antiviral effect, C viral hepatitis.*

1. Introduction

Statins, the inhibitors 3-hidroxi-3-metilglutaryl coenzyme A (HMG-CoA reductase), have a wide spread in the treatment of hypercholesterolemy.

Recent studies have demonstrated other effects of the statins. Thus, the simvastatin increases the hepatic production of nitric oxide, lowering the resistance at the level of hepatic sinusoids and attenuating the postprandial portal pressure in cirrhotic patients. For the patients with Nonalcoholic Steatohepatitis there are studies that show a lowering of the initially high levels of transaminases and diminished the degree of the hepatic steatosis [2].

More recently, in vitro studies have evidentiated the capacity of the statins to inhibit the replication of the Hepatitis C Virus (HVC). The Japanese researchers proved that this fact is not due to a cytotoxic mechanism, the destruction of the host cell, but is due to the inhibition of the viral RNA replication through a specific antiviral mechanism [1].

The replication of the HVC RNA and the assembly of the replicated complex need geranylgeranylation of one or more proteins. The HVC genome does not code a geranylgeranyl protein which suggests that the replication of the HVC needs a host cell, translated trough the increase of geranylgeranyl pyrophosphate synthesis in the host cell [4].

In some patients even if the viremia is undetectable after the interferon plus ribavirin treatment, the HVC may persist in the peripheral mononuclear cells long time after the apparent resolution of the C Hepatitis, which is associated with the

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increase of the geranylgeranyl pyrophosphate synthesis in the host cell. The antiviral mechanism of the statins can consist in the endogenous depleting of the geranylgeranyl pyrophosphate secondary to the inhibition of the mevalonate production (trough the inhibition of the HMG-CoA reductase) and geranylgeraniol [3], [5].

By comparing different types of the statins, it has been discovered that the antiviral activity is not equal: fluvastatin might have the strongest antiviral effect, atorvastatin and simvastatin have moderate effect, lovastatin has a weak effect and pravastatin has no antiviral effect [1].

There are studies in which the ribavirin has been replaced in the treatment with statins, the combination interferon plus fluvastatin being more efficient in the prevention of HVC RNA replication than interferon treatment or the combination interferon plus ribavirin [1].

2. Method

In this study have participated patients with HVC chronic hepatitis treated with alpha-interferon plus ribavirin does not show important cytolysis.

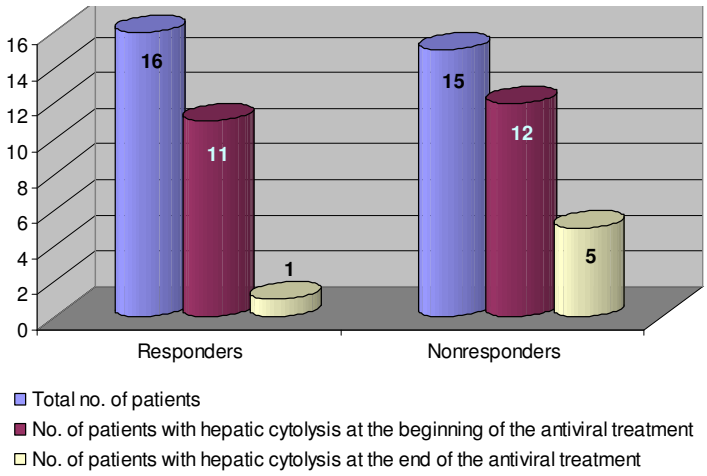

Fig. 1. *Cytolysis at the End of Treatment*

Exclusion criteria were values of 3 times higher than the normal value of transaminases, known hypersensitivity for any of the drug components (simvastatin), breastfeeding and pregnancy.

All the patients had the viremia determined at the inclusion in the study after which they were divided into two groups, one group treated with simvastatin for 3 months, 20 mg each evening, the other group not receiving any treatment.

The group treated was clinically examined and biochemically investigated after one week of treatment and after that every month. At the end of the treatment the hepatic biochemical samples and viremia of the two groups were compared.

3. Material

In our study were included 31 patients: 12 men (38.7%) and 19 women (61.3%) with ages between 34 and 65 years old.

All the patients have received antiviral treatment (interferon plus ribavirin) for 3 to 12 months prior.

From the 31 patients, 15 (48.4%) were nonresponders. These patients were treated between 3 and 8 months. The other 16 (51.6%) patients were responders after a treatment administrated for 9 to 12 months.

The duration from the end of the antiviral treatment to the inclusion in the study varied from 8 to 48 months.

4. Results and Discussions

At the beginning of the antiviral treatment the hepatic cytolysis syndrome was present at 23 (74.2%); among those 11(47.8%) being declared responders and 12 (52.1%) nonresponders at the end/ cessation of the antiviral treatment; From 8 patients without hepatic cytolysis at the beginning of the antiviral treatment, 5 (62.5%) are responders and 3 (37.5%) are nonresponders. The patients without hepatic cytolysis have a greater rate of response to the antiviral treatment, contrary to the literature data.

At the end of the antiviral treatment the hepatic cytolysis syndrome was present in only one patient among the responders (6.25% of 16 responder patients) and in 5 (30% of the 15 nonresponder patients) – Figure 1.

The normalisation of the transaminase values after the treatment with interferon and ribavirin is ascertained in responders and nonresponders, the response to the antiviral treatment being correlated with a higher rate of normalisation of the transaminase values.

At the inclusion in our study, all the patients had the quantitative determination of the viremias.

16 patients presented detectable viremias through the usual method. It is to be remarked that in according to the values of the viremias at the end/cessation of the antiviral treatment - 2 patients declared nonresponders had under the detection limit values of viremias and 3 patients considered responders presented detectable viremias, one of them being the patient who presented a hepatic cytolysis syndrome in the context of a negative viremia – Figure 2.

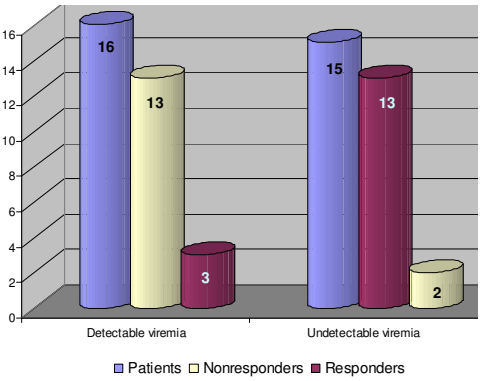

Fig. 2. *Viremia Values at Study Inclusion*

Among the 31 patients – 15 patients (48.4%) were included in the group which received 20 mg simvastatin in the evening, for three months and was initially monitored at one week after the beginning of the treatment and after that monthly by clinical and laboratory measurements: blood tests, GOT, GTP, bilirubin, alkaline phosphatase, Gamma-GT, electrophoresis, prothrombin index, cholesterol, triglycerides, glycemia and creatinine.

In the whole lot, at the inclusion in the study, the hepatic cytolysis syndrome was present in 10 (32.3%) patients, all being part of the nonresponders group. 11 (35.5%) patients from the whole lot presented hypercholesterolemia (values above 200 mg) at the inclusion in the study.

In the group of patients who had received simvastatin – the hepatic cytolysis syndrome was present in 5 patients (representing 50% of the total number of the patients with hepatic cytolysis syndrome in the moment of the study inclusion, with values three times higher than the normal value and 33% of the

patients who received statin as a treatment); 4 patients have hypercholesterolemia (representing 36.4% of the total number of the patients with hypercholesterolemia and 26.7% of the group of patients treated with statin).

Dependent on the viremia value, 7 patients treated with statin have the value of viremia under the detection limit (6 patients responders and 1 patient nonresponder with no detectable viremia at the inclusion in the study) and 8 patients have detectable viremias (6 patients nonresponders and 2 patients declared responders but with detectable viremias at the inclusion in the study). The age limits were 35-63 years of age and the gender repartition was 6 men and 9 women.

Under the treatment with simvastatin the values of the transaminases were modified as follows (Figures 3 and 4):

Fig. 3. *Evolution under treatment*

Fig. 4. *Evolution under treatment*

The hepatic cytolysis syndrome wasn't significantly modified, in only one case showing an important worsening of the hepatic cytolysis syndrome but even this did not pass the three fold of the normal value.

At the end of the 3 months of treatment the hepatic cytolysis syndrome was present in 6 (compared to 5 at the beginning of the treatment) patients treated with simvastatin from the 12 patients who repeated the blood test at that time. 2 patients who didn't have cytolysis at the inclusion in the study presented mildly elevated values of the transaminases (under two fold the normal value).

The values of the cholesterol was above 200 mg in 3 (20%) patients among those treated with simvastatin, the value in mg whereby the cholesterol lowered being smaller that the expected value; the average value at the inclusion in the study being 178 mg compared to 162 mg after three months of simvastatin treatment.

From the 15 patients treated with simvastatin 3 patients (20%) stopped the treatment before the 3 months mark, one to an allergic reaction and 2 at the family doctor's advice.

At the end of the 3 months of study, among the 27 (87% of the total patients included in the study) patients who had the viremia repeated, 13 were found with undetectable viremias. From these, 5 were treated with simvastatin and 8 had no treatment; in those not treated is being included one patient declared nonresponder with no detectable viremia at the inclusion in the study.

Among those with detectable viremias, 14 patients, there is a second nonresponder that presented no detectable viremia at the inclusion in the study and has follower the simvastatin treatment. In contrast with the patient that presented sustained no detectable viremias and was not treated with simvastatin, the former had a discrete hepatic cytolysis syndrome at the inclusion in the study.

The rest of 13 patients with detectable viremias, both at inclusion in the study and after 3 months can be divided as follows:

- From those treated with simvastatin (Figure 5): 4 presented increases in the absolute values of the viremias (one patient is declared responder with hepatic cytolysis syndrome at the end of the antiviral treatment with a detectable viremia at the inclusion in the study); 4 patients had lower values of the viremias.
- From those not treated with simvastatin (Figure 6): 2 presented increases in the values of the viremias; 3 presented a decrease of the values of viremias compared to the initial values.

It is to be mentioned that from the 4 patients who refused the second viremia measurement there are 2 patients responders with a detectable viremia at the inclusion in the study. If we analyse only the group of patients which presented a lowering viremia under the treatment with statins, we noticed that all of them had higher values of viremias (over 1,500,500) and the time passed from the end of the antiviral treatment is shorter compared with the other patients from the same group – Figure 7. No correlations were found when taking into consideration age, gender or the values of the hepatic cytolysis syndrome at the inclusion in the study.

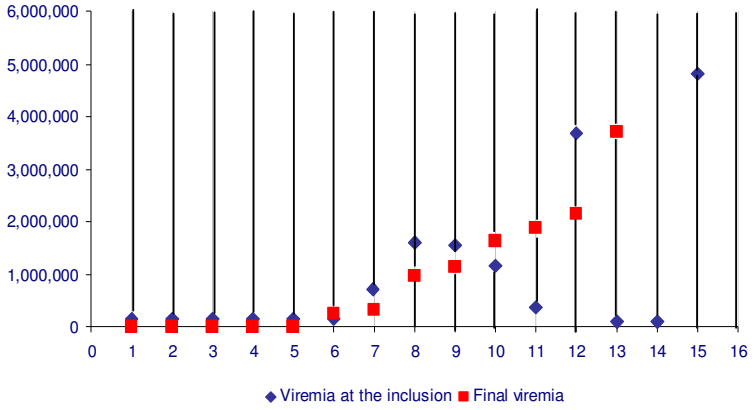

Fig. 5. *Viremias under Treatment*

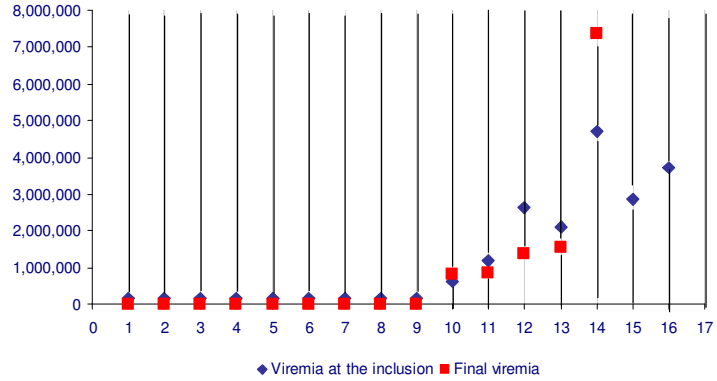

Fig. 6. *Viremias without Treatment*

5. Conclusions

1. The effects on the hepatic cytolysis syndrome are not important and are rare, not constituting a motive to forfeit the benefits of the simvastatin treatment as long as the transaminase levels are monitored, when this treatment is necessary.
2. The association of the statin treatment in patients with viral hepatitis C, immediately after the initiation of the antiviral treatment is a justified option.
3. The extension of the study groups will allow us to evaluate more rigorously the efficacy of statins.

Acknowledgments

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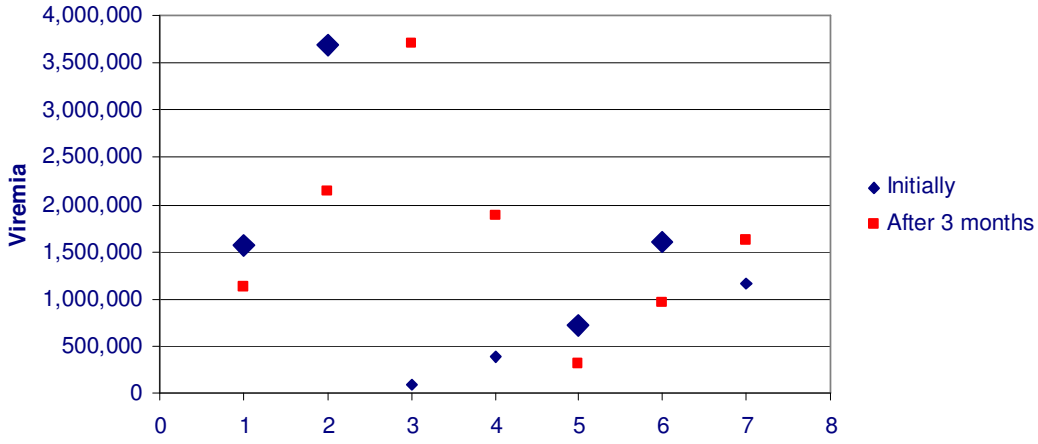

Fig. 7. *Viremias under Simvastatin Correlated With the Interferon Treatment*

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