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THE SAFETY OF LOVASTATIN IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

L. NEDELCU[1] O. ANDREESCU[1]
C. SCARNECIU[1] I. PANTEA[1]

Abstract: *The statins have a wide use in the medical practice, being considered first line of lipopenic agents. Also the statins pleiotropic effects and efficacy in non-alcoholic fatty liver disease are known, the most frequent adverse effect being represented by the increase of the transaminases. On a group of 28 patients with non-alcoholic fatty liver disease, treated 3 months with Lovastatin 20 mg, we followed the transaminases and bilirubin values at the beginning and at the end of the treatment. The patient with transaminases values over three times the upper normal values were not included. The obtained results show the non-inferiority of the Lovastatin reported to control. No adverse reactions were recorded, the transaminases values were maintained.*

Key words: *Non-alcoholic fatty liver disease, Lovastatin, safety.*

1. Introduction

The cardiovascular disease is one of the main mortality causes in the world.

The clinical trials have demonstrated that the LDL-Cholesterol reduction decreases the cardiovascular morbidity and mortality. The first line of lipopenic agents are the statins, considered in general safe and efficient in decreasing the LDL cholesterol and have an acceptable adverse effect profile [1]. This determines that, for the high cardiovascular risk patients the statins are representing a treatment standard, being considered as "life savers" for patients with stable or unstable atherosclerotic lesions [8], localized at coronary, cerebrovascular or peripheral level [2], being among the drug classes with the widest prescription [9].

At the recommendation of the NCEP Program (National Cholesterol Education Program) the more aggressive decrease of the LDL Cholesterol at patients with very high, high and moderate risk has determined the prescription of higher statin doses and/or the combination with other lipopenic agents, fact that raised the suspicion of increase in the toxicity/adverse effects of the statins [4]. These adverse effects are augmented also by the simultaneous use of other substances that have the same metabolic pathway of cytochrome P450 (e.g. antimycotic imidazoles, econazole, ketoconazole, erythromycin, clarithromycin, verapamil, amiodarone, nefazadone and high quantities of grapefruit juice) [1].

[1] Faculty of Medicine, *Transilvania* University of Braşov.

2. Material and Method

The study is part of the Excellence Research Grant, financed by the Ministry of Research and Education through the Medical Sciences Academy regarding the pleiotropic effects of the statins [5]. We have conducted 3 studies in parallel with the statins pleiotropic effects study at patients with known chronic liver disease (liver steatosis and chronic C virus hepatitis) monitoring also the modification of the hepatic cytolysis syndrome and cholestatic syndrome under treatment [6, 11]. The exclusion criteria were values higher than 3 fold the normal values for transaminases at the inclusion in the study or the known sensibility to the administered statin.

The patients with non-alcoholic fatty liver disease (NAFLD) were randomized in two groups:

- 28 patients treated with cu Lovastatin 20mg/day;
- 16 patients treated with Pentoxifilin 800 mg/day, considered as control group.

In total 44 patients were included, 20 women and 24 men with ages between 35 and 74 years.

We performed the statistical analysis of the transaminases and bilirubin evolution under treatment (initial values and after 3 months of treatment), the objective of this paper being the supporting of the safety of statin use for patients with chronic liver disease and finding an answer to the question if it is ethical for this group to be bereaved of the statins benefits.

3. Results and Discussions

The results obtained for the patients with NAFLD treated with Lovastatin for studies biochemical parameters were:

- For patients with normal ASAT values at the inclusion in the study, these values are maintained after three months with a statistically significant p (< 0.001);
- For patients with ASAT values higher than normal at the inclusion in the study, after three months the values decrease under treatment (p < 0.001), at 85% of those reaching normal values. (Fig. 1)

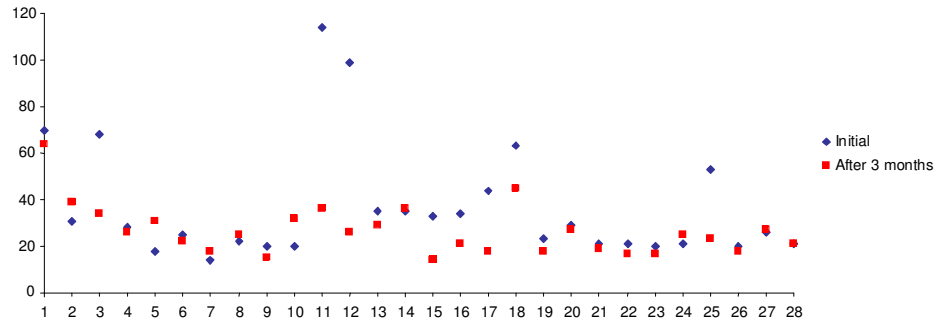

Fig. 1. *ASAT evolution for NAFLD patients treated with Lovastatin*

- For patients with normal ALAT values at the study inclusion these are maintained after three months (p <0,05);
- For patients with ALAT values over normal at the study inclusion, after three months the values decrease under treatment (p < 0.001). (Fig. 2)

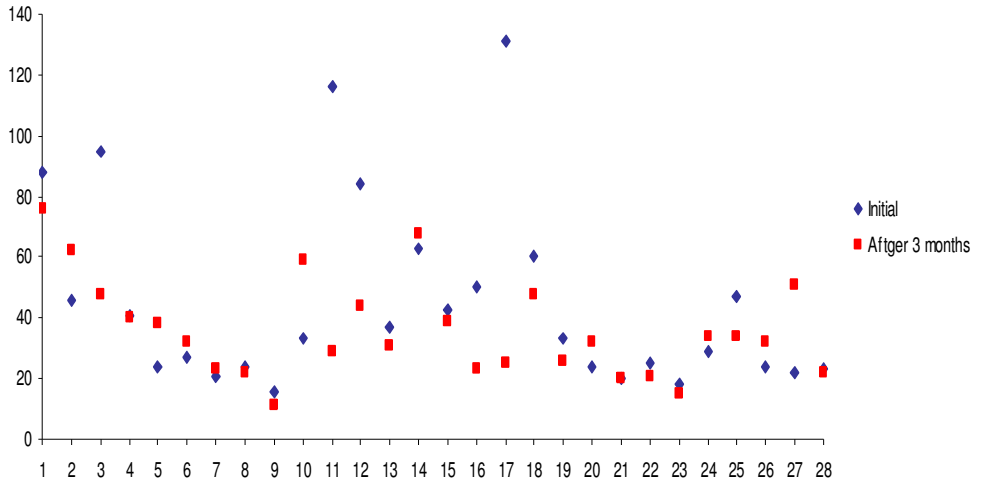

Fig. 2. *ALAT evolution for NAFLD patients treated with Lovastatin*

The statistical analysis of the cholestatic syndrome evolution at patients with hepatic steatosis treated with Lovastatin (L1L) revealed that:

- For patients with normal bilirubin values at the inclusion in the study the values are maintained after three months with p statistically significant ($p < 0.05$);
- For patients with high bilirubin values at the inclusion in the study the results are not statistically significant ($p > 0.05$). (Fig. 3)

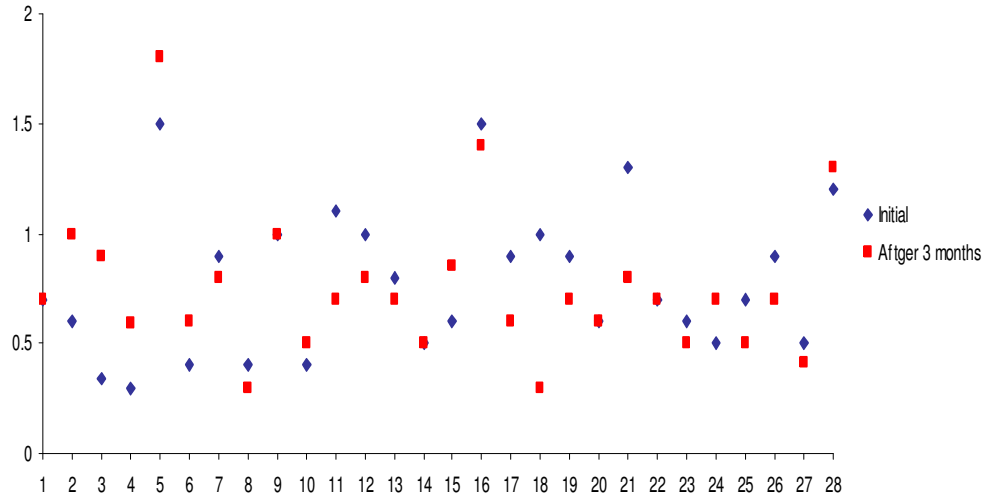

Fig. 3. *Bilirubin evolution for NAFLD patients treated with Lovastatin*

Comparing the obtained results with those of the control group treated with Pentoxifilin, drug considered efficient in hepatic steatosis, we observe a comparable evolution, favorable for the three biochemical parameters:

- For patients with normal ASAT values at the inclusion in the study these are maintained after three months with $p<0.05$;
- For patients with higher than normal ASAT values at the inclusion in the study, after three months these normalize under treatment ($p < 0.001$). (Fig. 4)

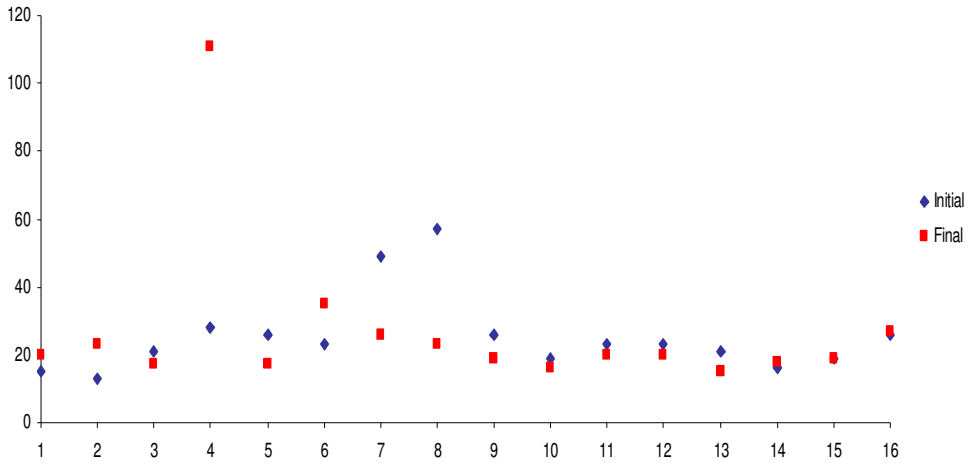

Fig. 4. *ASAT evolution for NAFLD patients treated with Pentoxifilin*

Similar results are obtained from the statistical analysis of the ALAT evolution under Pentoxifilin treatment (group LMs):

- For patients with normal ALAT values at inclusion these values are maintained after three months ($p < 0.05$);
- For patients with higher than normal ALAT values at inclusion, after three months these decrease under treatment ($p < 0.001$), normalizing. (Fig. 5)

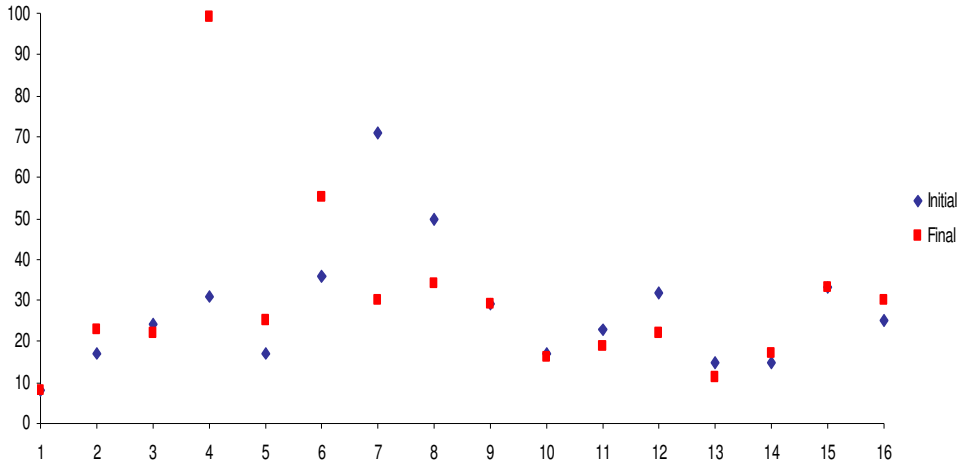

Fig. 5. *ALAT evolution for NAFLD patients treated with Pentoxifilin*

- For patients with normal bilirubin values at inclusion these are maintained after 3 months with statistically significant p ($p < 0.05$)
- For patients with higher than normal bilirubin values at inclusion the results were not changed. (Fig. 6)

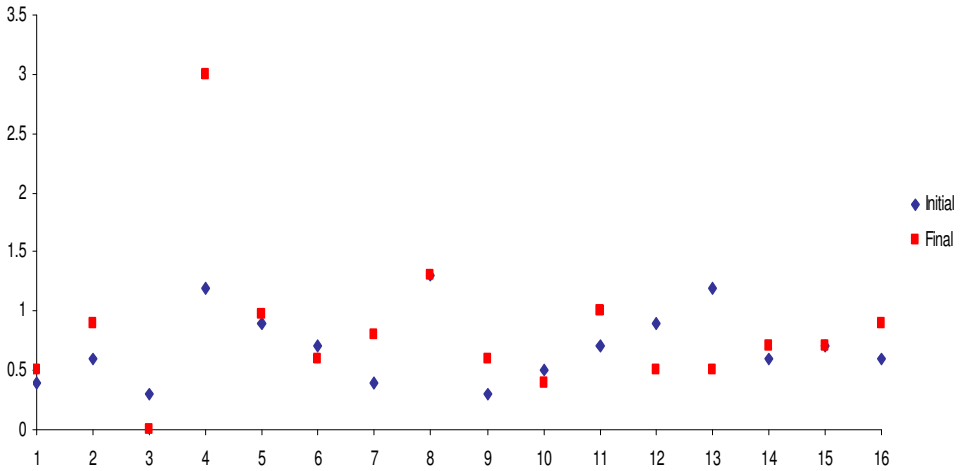

Fig. 6. *Bilirubin evolution for NAFLD patients treated with Pentoxifilin*

The most frequent adverse event is represented by the asymptomatic increase of the liver enzymes ASAT and ALAT, increase that is reversible at the discontinuation of the statin treatment and extremely rare is irreversible (1 in over 1000000 treated patients) [2]. By analyzing some statin clinical trials performed between 1966 and 2008 on 74102 patients, the relative risk reported to the increase of the transaminases as a consequence of the statin treatment was 4/1000 patients [1]. At higher doses of statins the risk increases, reaching < 1.3% for increases of transaminases at over three fold the normal values, in two or more consecutive measurements [1]. Until 1999 there were reported to FDA 30 cases of acute hepatic insufficiency due to statins, equivalent to 1 case /1000000 for every year of statin treatment. In the same time the general population risk for acute hepatic insufficiency is 1-2/ 1000000 persons [3].

The recommendations are to determine the transaminases before the treatment is started and after 12 weeks or at any dose increase and periodically for long term treatments. Moderate increases less than 3X normal values do not appear to induce significant liver toxicity in time [1] especially if there is no association with increase of the bilirubin [3].

Taking into account that the preexistent hepatic diseases are increasing the hepatic toxicity, FDA discourages the use of chronic hepatic diseases.

Taking into account this recommendation, approximately 25% of the adult Americans do not benefit from statins because is estimated that 20% of them have non-alcoholic fatty liver disease (NAFLD) – including a large spectrum of hepatic disease from hepatic steatosis, fibrosis, cirrhosis and hepatocellular carcinoma [10], and 5% may have chronic C virus hepatitis or cholestatic liver diseases [9].

In the same time there are studies suggesting that the NAFLD precedes the development of the metabolic syndrome, NAFLD representing a cardiovascular risk factor [12].

These facts are highlighting the necessity for studies that can establish if the chronic liver diseases represent an important risk for the hepatic adverse events which limit the use of the statins at this patient category, because this indication might be unethical for a patient group with high prevalence of cardiovascular risk factors [12].

There are published studies asserting that the patients with high levels of transaminases, with negative anti virus C antibodies, do not have a higher risk of hepatotoxicity compared with those without the hepatic cytolysis syndrome [7]. Furthermore, there is evidence that the patients with high transaminases have also fluctuating values outside the statin treatment. Same lack of liver toxicity was made obvious for patients with positive anti C virus hepatitis antibodies concluding that the statin therapy for chronic C virus hepatitis patients and hyperlipidemia is possible and safe [9].

These results sustain the recommendations from 2006 of the expert liver panel to National Lipid Association referring to the safety of the statins:

- The asymptomatic increase of the transaminases levels is a class effect of the statins and do to indicate a liver dysfunction;
- The liver insufficiency leading to death or requiring hospitalization

or transplant is very rare due to statins;

- The actual data do not sustain the routine monitoring of the hepatic enzyme levels at patients with statin treatment, e monitoring of signs and symptoms is recommended: jaundice, malaise, fatigability and bilirubin fraction analysis to determine the liver dysfunction more than ASAT and ALAT [2, 12];
- The current results are sustaining the use of statins for the treatment of hyperlipidemia of patients with non-alcoholic steatosis hepatitis and non-alcoholic fat liver disease, some small studies showing an improvement of the hepatic steatosis under the statins treatment [9].
- Decompensated cirrhosis or acute liver insufficiency represent a contraindication for the statins treatment[12];

As a conclusion it seems that it is safe to administer statins to patients with preexistent liver disease when there is indication due to the presence of hyperlipidemia or cardiovascular diseases [9].

3. Conclusions

1. Lovastatin can be administered safely to patients with NAFLD disease having indication for this treatment;
2. Lovastatin improves the hepatic cytolysis syndrome in NAFLD;
3. Is not ethical to deprive of statin treatment the patients with NAFLD that have indication for this treatment.

Accepting that our results are obtained on small patient groups, we endorse other specialty references that the statins must be administered when are indicated for patients NAFLD without being afraid of notable adverse effects.

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