TIME-DEPENDENCE OF HYPOLIPEMIC STATIN EFFECTS

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VREMENSKA ZAVISNOST HIPOLIPEMIJSKIH EFETATA

STATINA

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INTRODUCTION

Lipids are heterogeneous organic units whose basic physical characteristic is that they can not be dissolved in the water. In the circulation they exist in a form of lipoprotein molecules which differ among each other in lipids and apoprotein content and they can be divided in 5 fractions: chylomicrons, very low density - VLDL, intermediate density-IDL, low density-LDL and high density-HDL lipoproteins (1).

Hyperlipidemia is a disorder of lipid metabolism, with consequential increase of their quantity in the blood and their piling up in the organism. The criteria for diagnosis is triglyceridaemia higher than 2.2 mmol/l and/or cholesterolasma higher than 6.2 mmol/l, measured 14 hours after the last meal (1). They are divided into primary (which according to Fridricson can be further divided into 6 types) and secondary (1). However, only types II and III are clinically manifested by fast developing atherosclerosis.

Hyperlipoproteinaemia treatment has for its goal slowing down the development of atherosclerosis via diets, drugs and surgically (1). Treatment with drugs is application of different hypolipemics. Statins (lovastatin, simvastatin, pravastatin), fibrates (gemfibrozil, bezafibrate), niacin and resins (colestipol, cholestyramine, pravastatin) are at disposal. On using these drugs, we aim to normalize serum cholesterol and triglyceride levels to reduce the risk of developing cardiovascular disease. In the treatment of hyperlipidemia, statins play a key role.
vastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin) are specific reversible inhibitors of HMG-CoA reductase, key enzyme in endogenous cholesterol synthesis, and they are considered to be the most powerful hypolipemiacs (2).

Pharmacokinetics of statins shows that after the resorption from digestive tract, they are being rapidly eliminated via bile. Primarily, they concentrate in the liver, so that systemic exposure is very low. Half-time of the statin elimination is short, but their pharmacologically active metabolites are excreted for 24 hours. Pharmacological effects are evident after 2 weeks of application of the drugs, while the maximum effect is achieved after 4–6 weeks (2, 3).

Drug dosage is individual and depends upon existence or non-existence of coronary disease (2). The indication is coronary disease and types II, III and IV of hyperlipoproteinemia. Contraindications are sensitivity to drugs, acute hepatitis, persistent increase of aminotransferases, renal failure, pregnancy and breastfeeding, alcoholism and drug addiction (2).

The most common adverse effects are typical gastrointestinal problems and insomnia. Rarely there is appearance of liver and skeletal muscle damage, from myalgia to rhabdomyolysis (2).

PATIENTS AND METHODS

The clinical study involved 74 patients with hyperlipoproteinemia type II and III, 59 patients with coronary disease and 15 without, of both sex (Table 1). The research was done in Department of Cardiology, University Center "Kragujevac", for 3 years period, 2000–2003. The aim of the study was to determine the time-dependent effect of statin therapy, especially time necessary to achieve target value of lipoprotein profile. Having in mind the pharmacological effects of statins, the research was carried out: before therapy, after 2 and 6 weeks, 3 months, and than every 3 months in a cumulative period of 2 years of therapy.

According to the Rote list (4), and in accordance to the leading world studies (5–7), the patients have been treated with statins, 70 with atorvastatin, 4 with simvastatin. The dosage depended upon the presence of the coronary disease. With patients who suffered coronary disease initial dose was 20 mg daily, and dose adjustment was done in the intervals of 4 weeks, up to the dosage of 80 mg daily. Patients without coronary heart disease were treated with 10 mg daily (2, 5, 7).

The criteria for the dosage reduction, but not for the exclusion from the study, were: tenfold increase of creatin-phosphokinase value or persistent threefold increase of aminotransferase, as well as the decrease of the total cholesterol under 3.6 mmol/l or LDL-cholesterol under 1.94 mmol/l. Exclusion criteria were: renal failure, acute hepatitis, myopathy, rhabdomyolysis (2, 7). The following parameters of the statins effect were followed: total cholesterol (TC), LDL-cholesterol (LDL), HDL-cholesterol (HDL), triglycerides, atherogenic indexes UH/HDL and LDL/HDL. The time necessary to achieve target value of lipoprotein profiles was measured.

For the achievement of the target values the criteria of EAS and NCEP were used which are considered the “guidelines” in the therapy of hyperlipoproteinemia and coronary disease (1, 8, 9). The target values of lipoprotein profile, by EAS, were dependent upon different factors, among which the key risk factor was coronary disease (1). As the presence of family history of hyperlipoproteinemia is the sufficient reason to fall under the high-risk-factor group, all patients were classified into the given group and had the desired UH value of 4.5–5 mmol and LDL of 3–3.5 mmol. According to the suggestions from NCEP, the desired value of LDL the level of 2.6 mmol/l was taken with patients with coronary disease, 3.35 mmol/l when one or two risk factors for coronary disease were present and 4.15 mmol/l with patients without risk factors (1, 8, 9). Out of methods of inferential statistics, one way ANOVA have been applied.

Table 1. Demographic and clinical characteristics of patients.

<table>
<thead>
<tr>
<th>Age</th>
<th>30–55 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>59 male, 16 female</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>59 with coronary disease, 15 without</td>
</tr>
<tr>
<td>Levels of aminotransferases</td>
<td>AST 22.9±5.8 U/L, ALT 19.0±6.9 U/L</td>
</tr>
</tbody>
</table>

RESULTS

The statins significantly reduced the level of total cholesterol, the effect being more prominent in time (One-way ANOVA; p=0.000). Highly significant difference has been registered after only 2 weeks of application of these drugs, more significant after 6 weeks, the most significant after 3 months. From the 3rd month up to the end of the 2nd year, there was no statistically significant change of the parameter value (Figure 1).

The same significant trend was observed for the LDL- and HDL-cholesterol (with registered increase of HDL), and atherogenic indexes UH/HDL and LDL/HDL. The similar trend of the statistically significant reduction was observed for the triglycerides, but the most significant change was registered later, only after the six-month’s period (Figure 2–6).
The highest registered average value of the total cholesterol reduction under the statin effects after three-month therapy was 38.1%. The highest percentage of the change in value of total cholesterol was 61.67% (in the period of 1, 5 to 2 years). After 6 weeks of continual statin therapy 23% of patients has reached the target value of the total cholesterol. In the period of 6 weeks up to 3 months 58.1% of patients have reached the target value of this parameter, and the desired trend continued, so that at the end of the two-month period, all patients achieved the target value of the total cholesterol.

The highest average percentage of the change in value of LDL-cholesterol in relation to the value before the therapy was recorded after 18 months of therapy and it was 48.07%.

When the time of achieving the target value of LDL-cholesterol was analyzed, the two criteria were used: EAS and NCEP. In accordance to the EAS criteria, the target value of the LDL-cholesterol, after 6 weeks of statin therapy was recorded with 21.6% patients. After that period, the same trend was continued, so that at the end of 3 months of statin therapy 93.2% of patients have had the target value of LDL-cholesterol, and at the end of 9 months therapy period, all patients have reached the target value.

Achieving the target value of the LDL-cholesterol in accordance to NCEP criteria was somewhat slower, but it was achieved with longer statin therapy. Six weeks after
the application of these drugs, the target value of LDL-cholesterol was recorded only with 2.8% patients. In the period between 6 weeks to 3 months, target value was achieved with additional 69.4% of patients. The above mentioned trend was continued, so that after the one year period of drug application, the target value was recorded with 97.2% of patients. After two year period, only two patients did not achieve target value of LDL-cholesterol in accordance to these criteria.

In accordance to both criteria, the same time period of the achievement of the target value of LDL-cholesterol was recorded with 55.6% patients after 6 weeks, and 54.2% after 3 months.

The highest average change of HDL-cholesterol was 12.5%. The target value of HDL-cholesterol, with statin therapy, was achieved with half of the patients. The highest number of patients, 44.4% has reached the target value by the end of the 3rd month. The rest 5.6% of patients has achieved the target value by the end of the 2nd year of therapy.

The highest change in the value of triglycerides was recorded after 2 years of statin therapy and on average it was 38.35%. Even 44.6% of patients had the target value of triglycerides prior to the therapy. During the first two weeks of statin therapy, 6.8% patients achieved the target values. In the period between 2nd and 6th week, the target values were recorded with additional 17.8% patients, while in the period between the 6th week and up to the 3rd month, as well as in the period between the 3rd and the 6th month of therapy, the target value achieved another 11% of patients. It means that after half year of therapy 91.8% of patients achieved the target values of the parameters observed. This trend was continued, so that after 2 years of therapy, 100% of patients achieved the target value of triglycerides.

An average reduction in value of atherogenic index UH/HDL was 46%, and for LDL/HDL 53.86%, after 3 months of statin therapy. With over 90% of patients during the first year of the statin therapy, the target values of index UH/HDL were achieved. Prior to therapy 1.4% of patients had target value of the parameter observed, and with statin therapy this number was slowly increasing, so that in the period of 6 weeks up to three 3 months, with 57.7% of patients, the target values of this index have been achieved. This trend have continued, and after 9 month 97.2% of patients had achieved the target value of this parameter, and by the end of the therapy the number of patients amounted up to 100%.

After 3 months of statin therapy, more than half of the patients (67.6%) have had the target value of the index LDL/HDL, while the highest increase in the number of patients (52.7%) with target values of the parameter observed was noted in the period between 2nd week and the 3rd month, and than it was noted in the period between 3rd and 6th month (10.8%). In the following period of the year and a half, the patients with whom the target value was achieved were recorded only as the individual cases, so by the end of 2-years period of statin therapy, 85.3% patients did achieve the target value of the index LDL/HDL.

**DISCUSSION**

The contemporary studies show that cardiovascular diseases are responsible for up to 50% of the mortality rate. Cardiological studies, besides the morbidity and mortality rate pre and post „statin era“ (7), point out the significance of these drugs in the secondary cardiovascular disease prevention. The studies dealing with correlation of hyperlipoproteinemia and atherosclerosis indicate that the degree of the reduction of the risk of coronary disease (3) depends on the degree of the reduction of the LDL-cholesterol, as the most atherogenic one.

There is lot of another studies which studied statin effects, but they analized effects of aggressive hypolipemic treatment, or treatment with unique dose for all patients.

In our study, the patients have been using atorvastatin and simvastatin as the most commonly prescribed statins around the World, with excellent safety profile and efficiency (11). The dosage depended upon the presence of the coronary disease (2, 5, 7). Statin therapy led to the statistically highly significant time-dependent change in the level of all lipoprotein parameters analyzed. The effects mentioned above were registered after two weeks of statin therapy, which correlates to the time of the appearance of the first pharmacological effect, and even than it had shown the high statistical significance. The changes were more distinct after 6 weeks of therapy, which correlates to the period of the maximum therapeutic effect of statins (2, 3). After 3 months of application of these drugs, the changes were the most significant, which correlates to the time period of the maximum effect of the hypolipemics (3). The effect achieved during the continual period of therapy stays constant, that is to say, with adequate dosage the effect is successfully maintained. Only for triglycerides, the statin effect is the most intensive after six months.

The study proved statistically highly significant effect of statins in relation to the decrease of cholesterol level on average up to 38.1%, in relation to the decrease of LDL-cholesterol up to 48.07%, and increase of LDL-cholesterol up to 12.5%, and reduction of triglycerides up to 34.7%.

The results of our study match the results of other studies which studied statin effects. CURVES study (1) emphasized the superior effect of atorvastatin, which reduced in the two-month period the level of the LDL up to 35–61% and triglycerides up to 19–37%, depending on the dosage. MIRACL study shows that this drug in the period of 16 weeks reduces the level of LDL by 40% and of triglycerides by 16%, with highly aggressive hypolipemic approach (12).

Other studies indicated the possibility of the reduction of the total cholesterol up to 23% and LDL up to 30–44%, under the effects of simvastatin (4, 5, 7). In the year 2002, rosuvastatin is being mentioned for the first time as potentially the most powerful of all. The STELLAR study 2003 (7) is the first clinical study which compared the effects of this statin with others, pointing out its change in the level of LDL as well as faster achievement of the desired values.
In our study, an average value reduction of the UH/HDL after the three-months statin therapy was 46%, and for LDL/HDL 53.86%. These results had been compared with the results of other studies (5, 7) in accordance to which atorvastatin reduced the index level of UH/HDL by 46% and LDL/HDL by 85%, but with highly aggressive approach. Rosuvastatin reduced the value UH/HDL by 69% and LDL/HDL by 95% (7). These indexes are independent risk factors for atherosclerosis. The studies show that patients with index LDL/HDL > 5 have concomitant coronary disease, while patients with value < 5 do not have (11).

The period in which the target values of lipoprotein fractions can be achieved, according to the results of our study, is longer than period of appearance of pharmacological statin effects, and it amounts up to 3 to 6 months. In addition, the target value of total cholesterol after three-months therapy was achieved with 81.1% patients, and after the same time period, the target value of LDL was achieved with 93.2% patients in accordance to EAS criteria, and 72.2% in accordance to NCEP criteria. During the same time period 44.4% of patients have achieved the target value of HDL, and 80.8% the target value of triglycerides. In conclusion, almost the half of the patients achieved the target values of all parameters observed after 3 month therapy, over 90% patients after 6 months therapy, but only if the value of HDL was not taken into account, because after this period the target value of this parameter achieved only 50% patients.

The 100% achievement of the target values of lipoprotein parameters was made possible by continual statin therapy, and all this for the value of the total and LDL-cholesterol according to EAS criteria, after 9 month therapy, while in accordance to the NCEP criteria the value could not have been achieved, keeping in mind that the criteria are very high (1, 8, 9). Statins have the possibility of 100 % achievement of the target value of triglycerides and index UH/HDL, but for the longer period of two years.

In our study, 23% of patients achieved the target values of the total cholesterol after 6 weeks of therapy. In the period between 6 weeks and 3 months, the target value was achieved by additional 58.1% patients, and by the end of the 9 months, all of patients had achieved the target value of total cholesterol.

In accordance to EAS criteria, the target value of the LDL, after 6 weeks of statin therapy was noted with 21.6% of patients. In the period between 6 weeks and 3 months, the target value had been achieved with additional 71.6% of patients, so that by the end of this period 93.2% of patients had the target values achieved, and at the end of the 9 months, all of the patients have achieved it. The achievement of the target values of LDL, in accordance to NCEP criteria, was slower having in mind that these are the highest criteria. As these criteria are being considered as the clinical «guidelines» in hyperlipoproteinemia therapy (4, 7, 9), they are considered to be the imperative. Six weeks after statin therapy, the target value of LDL was recorded with only 2.8% of patients. In the period between 6 weeks and 3 months, the target value achieved the additional 69.4%. The above trend continued, so that after one-year therapy, the target value was recorded with 97.2% of patients. By the end of study, the target values have not been achieved with two patients.

All in all, the same rate at which the achieving of the target values of LDL occurred, in accordance to the both criteria, was recorded with 55.6% of patients, after 6 weeks of therapy, and with 54.2% after the period of 3 months. During the overall observation period, the possibility of the 100% achievement of the target value of LDL-cholesterol can be registered only in accordance to the EAS criteria, after 9 months therapy period, but not in accordance to NCEP criteria. For the achievement of the target values the criteria of EAS and NCEP were used which are considered as the "guidelines" in the therapy of hyperlipoproteinemia and coronary disease (1, 8, 9). This and other studies, used the "gold standard", like IAS criteria from the end of 2004 year (target level of LDL-cholesterol < 2.6 mmol/l).

The target values of HDL were achieved with half of the patients during the overall observation period, out of which 36.3% achieved it after three-month therapy period.

The target values of triglycerides were achieved with 80.8% of patients after the 3 months statin therapy, and 91.8% after 6 months therapy, but 44.6% of patients had target values even prior to therapy. After 2 year period of statin therapy, the target value of triglycerides was reached by 100% of patients.

After 3 months therapy 84.5% of patients reached target values of UH/HDL, and 67.6% of LDL/HDL. After 6 months of therapy, 93.8% patients achieved the target value of UH/HDL, and 78.4% of LDL/HDL. So, over 67% of patients had achieved the target values of both atherogenic indexes after 3-month therapy, and 78% after 6 months.

In conclusion, for majority of the observed parameters, the period of the achievement of the target values was 3–6 months. This is longer than in other studies (7) which we can explain with the fact that the target values used in our study were very high, and also, the principles of the very aggressive hypolipidemic therapy were not being applied.

Thus, GREACE study used the therapy approach similar to the one applied in our study, showing that with atorvastatin target value of LDL is being reached with 95% of patients, and of total cholesterol with 97% (5). MIRACL study shows that with atorvastatin the goal value of the total cholesterol is being reached with 83% patients with 10 mg dosage (12). STELLAR study (7) shows the possibility to achieve the target values of LDL in accordance to the NCEP (9) with rosuvastatin in 80%, and with atorvastatin in 70% of patients.

The period of reaching the target level of LDL-cholesterol matches the EAS results, which indicates that with statin therapy target level can be reached in 3 months (2–4).

In conclusion to the above-mentioned, it can be concluded that with statin therapy the maximum hypoli-
pemic effect is achieved in 3 months, while the goal parameter values of lipoprotein profile can be achieved in the period of 3–6 months, and for many of the parameters to the extent of 100%.

In conclusion, statins show significant effect on all parameters of lipoprotein profile, including the atherogenic indexes, by continual three-months therapy. The statin effect is dependent upon the time factor. Pharmacological statin effect is registered after 2 weeks of their application, intensifies after 6 weeks, and it is the most distinct after 3 months. After achieving the maximum, hyperlipemic effect after the three-months therapy stays constant. The target values of lipoprotein profile can be achieved in the period between 3–6 months of statin therapy. It is possible to achieve 100% of target values of some lipoprotein parameters by continued statin therapy.

REFERENCES