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Effectiveness and safety evaluation in the dyslipidemia treatment with statins

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ABSTRACT

Statins are used to reduce morbidity and mortality in patients with a high risk of cardiovascular disease. However, the use of statins does not ensure effectiveness and pharmacotherapeutic safety. In this context, the present study aimed to evaluate the effectiveness and safety of the therapy with statins in patients with dyslipidemia and high cardiovascular risk. To evaluate these parameters, this study selected 113 dyslipidemic patients with regular statins use of at least seven months. It was an observational cross-sectional study, based on data analysis collected from biochemical tests of patients with dyslipidemia in the public health system in the state of Pernambuco, Brazil. Isolated hypercholesterolemia was the most prevalent dyslipidemia type and the most used statin was atorvastatin (84%), followed by simvastatin (16%). The study observed no effectiveness in 58.4% of the patients; 28% had no safety in the treatment, and 48.3% were using doses above the standard dosage. Comparing effectiveness and safety between the same drugs, at standard dosage with higher dosages, there was not any statistical difference in biochemical test results. Therapeutic goals for LDL-C ≤ 70 mg/dL were found in 28% of cases. However, the use of doses above the standard dosage intended to reach very low LDL-C levels should be reevaluated, since there was no statistical difference in reducing the lipid profile, suggesting that the same results can be obtained with a lower standardized dose. This study provides data relevant to the discussion of statins use and to the necessity of strengthening pharmacotherapeutic monitoring in dyslipidemia treatment.

Keywords: Dyslipidemias. Drug Monitoring. Evaluation of Results of Therapeutic Interventions. Hydroxymethylglutaryl-CoA Reductase Inhibitors.

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INTRODUCTION

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) structural inhibitors, an enzyme that limits liver cholesterol biosynthesis, resulting in up regulation of LDL (low density lipoprotein) receptors, which leads to decreased levels of LDL-C and, consequently, to reductions in cardiovascular mortality (Scandinavian Simvastatin Survival Group, 1994; Heart Protection Study Collaborative Group, 2002).

Cholesterol and triglycerides are lipids generally associated with plasma lipoproteins and its accumulation leads to dyslipidemia. Atherogenic lipoproteins (LDL, IDL, VLDL, chylomicron remnants) in increased levels are considered one of the main risk factors of injury to vascular endothelium and of atherosclerotic plaque formation, as well as hypertension and smoking (Kouromichakis *et al*., 2011; Xavier *et al*., 2013).

In Brazil, in 2010, chronic non-communicable diseases (NCDs) accounted for 73.9% of deaths, whose main causes were cardiovascular disease (Duncan *et al*., 2012). In recent years, the NCDs have come to represent 69% of hospital spending in the Unified Health System (SUS) and are responsible for high frequency of hospitalizations. In 2007, there were approximately 1.2 million hospitalizations for cardiovascular diseases, resulting a total cost of about R$ 1.5 billion and a total of 91,182 deaths (Ribeiro *et al*., 2012). In Recife, the city where the present study was performed, the circulatory system diseases are the major death cause among the elderly, with a mean mortality rate of 189 deaths per ten thousand inhabitants (Silva *et al*., 2008).

The main risk factors for cardiovascular disease are hypertension, obesity, sedentary lifestyle, poor eating habits, smoking, alcohol consumption, insulin resistance and dyslipidemia (Schmidt *et al*., 2011; Pellanda, 2011).

Large randomized controlled trials results have indicated that statin therapy significantly reduces the cardiovascular risk events in high-risk patients (Scandinavian Simvastatin Survival Group, 1994; Shepherd

et al., 2002). The benefit in reducing this risk has also been found in clinical-practice setting (Wei *et al*., 2005; Amarenco & Labreuche, 2009; Sirimarco *et al*., 2014).

Several studies confirm that the use of standard statins dosages (lovastatin 40 mg, simvastatin 20 mg, atorvastatin 5-10 mg and pravastatin 40-80 mg) reduces total mortality, coronary mortality and cardiovascular morbidity in secondary prevention patients (Sacks *et al*., 1996; Ballantyne *et al*., 1998; LIPID Study Group, 1998; Infac, 2005).

According to Andrés and Zubicaray (2008), statin therapy would only be effective in the secondary atherosclerotic or cardiovascular diseases prevention in patients with risk of high cholesterol levels. There are several ways to stratify this risk, but the method indicated by the Brazilian Society of Cardiology (Xavier *et al*., 2013), Brazilian Health Ministry (Brazil, 2013) and Spain (Marrugat *et al*., 2007) is the Framingham Risk Score.

In clinical practice, cardiovascular risk stratification is based on the individual assessment risk factors (Holewijn *et al*., 2010). Therefore, the Framingham Score is used for this stratification, identifying, in cost-effectiveness terms, patients with highest risk levels, who could benefit most from statin therapy (Pletcher *et al*., 2009).

The Brazilian Health Ministry distributes statins for free for the treatment of dyslipidemia in patients with high cardiovascular events risks (Brazil, 2013).

Statins are effective and considered an important therapeutic strategy, but the use of these drugs does not ensure effectiveness or safe treatment. In this context, the present study aimed to evaluate the effectiveness and safety of the therapy with statins in patients with dyslipidemia and high cardiovascular risk, inside a high complexity public pharmacy of the State Secretary of Health in Pernambuco, Brazil.

MATERIAL AND METHODS

Study design

It was an observational cross-sectional study, based on the data analysis collected from biochemical tests patients' with dyslipidemia in the public health system in the state of Pernambuco, Brazil (Hochman *et al*., 2005). Only exams of patients who had used statins for at least seven months were considered, once the Brazilian Health Ministry recommends biochemical monitoring every six months (Brazil, 2013).

Data collection, for simple random sampling occurred from November 2009 to January 2010 (Mattar, 1999). After collection, the pharmacotherapeutic results regarding effectiveness and safety were analyzed.

Study Site characteristics

The research was conducted in a high complexity public pharmacy of the State Secretary of Health, located in Recife, Pernambuco, Brazil. In this pharmacy, free drugs are distributed by the public health system, with an average attendance about 15,000 users with high complexity diseases per month, with approximately 10% of patients with dyslipidemia.

Criteria for inclusion in the study

Patients who were registered in the public state pharmacy as having dyslipidemia and who had received atorvastatin or simvastatin regularly for at least seven months without interruption or treatment discontinuation were eligible for inclusion in the study.

Those patients who had no biochemical tests required by the local legislation until the beginning of the study, in addition to those who discontinued receiving the drugs on the scheduled dates during the seven months prior to the study, were excluded from the study (Brazil, 2013).

Study Sample

In order to determine the sample size, 1,500 patients were taken as the study universe, with 10% expected prevalence estimation, criteria inclusion effect of 10% (150 patients) and a 5% sample error in 95% confidence interval (Barbetta, 2002).

The sample was composed of 113 statin users of both genders and different ages, with registration and monitored documentation, which met the inclusion study criteria. In the submitted documents, the biochemical laboratory exams conducted to monitor treatment, as required by the local legislation, were recent, and they presented the lipid profile (LDL-C, HDL-C, triglycerides and total cholesterol), total creatine kinase (CK), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

Biochemical parameters

The data of the biochemical tests were evaluated using the reference values specified by the Brasilian Health Ministry (Brazil, 2013), which specifies the targets for dyslipidemia therapy. These values corroborate with the IV Brazilian Guideline for Dyslipidemia and Atherosclerosis prevention from the Department of Atherosclerosis of Brazilian Society of Cardiology (2007), as well as Pharmaceutical Care Practice: the Clinician's Guide, which evaluates drug therapy effectiveness and safety (Cipolle *et al*., 2004).

Therefore, therapy was considered ineffective when the lipid profile presented LDL-C $\geq$ 100 mg/dL values (considering the high risk stratification), triglycerides > 200 mg/dL, total cholesterol > 200 mg/dL and HDL-C $\leq$ 40 mg/dL. Similarly, the following were considered unsafe therapeutic total CK values: > 170 U/L, ALT > 40 U/L (men) and > 35 U/L (women), and AST > 40 U/L (men) and > 30 U/L (women).

Ethical aspects

The present study was initiated after approval by the Ethics Committee of Federal University of Pernambuco under the number CAAE 0031.0.172.000-09 in accordance with resolution No. 196/96 of the National Health Council.

Table 1 - Unpaired t-test comparing atorvastatin and simvastatin users, biochemical exams (Mean ± SD) stratified by medicine at different dosages, after at least seven months of treatment (CI, 95%), Recife, PE (n=113)

Variables	Atorvastatin 10/20/40 mg (n = 95)	Simvastatin 20/40/80 mg (n=18)	p
Total cholesterol (mg/dL)	175.55 ± 7.41	157.12 ± 15.73	0.0174
HDL-C (mg/dL)	51.13 ± 2.56	47.68 ± 5.70	0.1287
LDL-C (mg/dL)	89.68 ± 5.63	86.09 ± 16.06	0.3306
TG (mg/dL)	170.38 ± 22.92	132.54 ± 22.80	0.0086
CK (UI/L)	134.24 ± 18.29	141.19 ± 42.20	0.3763
AST (UI/L)	23.48 ± 1.64	22.53 ± 2.24	0.2408
ALT (UI/L)	26.20 ± 3.18	19.00 ± 3.11	0.00067

Note: $p \leq 0.05$ indicates statistically significant difference.

To participate in the study, each participant had to sign an informed consent form.

Statistical Analysis

Data were processed and analyzed using the SPSS 11.5 software system and Microsoft Excel 2007. Data description consisted in the variables quantitative analysis by means with a 95% confidence interval ($p < 0.05$), and frequency distribution for categorical variables. Means were compared using the unpaired t-test ($p < 0.05$).

RESULTS

Users' profile

In this study, 65 (57.5%) of the 113 users were elderly (≥ 60 years) with mean age of 62.6 ± 9.8 years and 68 (60.2%) were female.

Concerning the types of dyslipidemia observed, isolated hypercholesterolemia was detected in 109 (96.5%) and mixed hyperlipidemia in 4 (3.5%) users.

Statins prescriptions profile

Among the evaluated users, 95 (84.1%) were taking atorvastatin and 18 (15.9%), simvastatin. Among the prescribed dosages, 5 (4.4%) users were taking atorvastatin 40 mg/day, 34 (30.1%) were taking 20 mg/day and 56 (49.6%) were taking 10 mg/day. For simvastatin, 3 (2.7%) users were taking 20 mg/day, 14 (12.4%) were taking 40 mg/day and 1 (0.9%) was taking 80 mg/day.

Effectiveness treatment profile

It was found that 66 (58.4%) users did not show efficacy during treatment, of which 11 were using simvastatin (61.1% simvastatin users) and 55 were using atorvastatin (57.9% atorvastatin users).

Among these 66 users with ineffective treatment, 30 (45.5%) had LDL-C ≥ 100 mg/dL and 10 (15.2%) presented LDL-C ≥ 130 mg/dL. In addition, 28 (42.4%) users had triglycerides values > 200 mg/dL; 23 (34.9%) had total cholesterol value above 200 mg/dL, and 26 (39.4%) showed HDL-C ≤ 40.

Regarding the LDL-C, 32 (28.3%) in 113 users presented LDL-C levels ≤ 70 mg/dL, and 52 (46.0%) had LDL-C levels between 70 mg/dL and 100 mg/dL.

Table 1 presents the effectiveness results obtained after at least seven months of related statin use, according to specified medicines.

Safety treatment profile

It was observed in this study that 24 (21.2%) users presented total creatine kinase values (CK) > 170 U/L. This group had a mean age of 62.7 ± 9.7 years, of which 13 users (54.2%) were using dosages above the standard scales.

Regarding the liver transaminases, 11 (9.7%) users had high AST levels, two of which were men (AST> 40 U/L) and nine of which were women (AST> 30 U/L). The mean age group was 61.5 ± 7.5 years, and the average AST level was 39.9 U/L. The doses use above the standard scales was observed in five (45.5%) users. Ten users had high ALT levels. Specifically, two men had ALT> 40 U/L and eight women had ALT> 35 U/L. The average group age was 59 ± 6.7 years, and the ALT levels were 56.7 U/L and dosages exceeding the standard scales were detected in 4 (40%) users.

The same Table 1 presents the safety therapeutic results obtained after at least seven months using statins, according to specified medicines.

Effectiveness and safety comparison

The effectiveness and safety profile treatments were compared. First, a comparison was made between the results of patients taking atorvastatin and simvastatin. The results are depicted in Table 1.

Next, the effectiveness and safety profiles were compared between the same drugs, at different dosages: Standard dosages vs Higher dosages. The results are presented in Tables 2 and 3.

DISCUSSION

The obtained results show that most patients with dyslipidemia were elderly and female, with a prevalence of isolated hypercholesterolemia. This result is consistent with other studies conducted in Spain (Andrés & Zubicaray,

Table 2 - Unpaired t-test comparing simvastatin users at standard dosage with higher dosages and the laboratorial exams results, after at least seven months of treatment (CI, 95%), Recife, PE (n=18)

Variables	Simvastatin 20 mg (n = 3)	Simvastatin 40/80 mg (n=15)	p
Total cholesterol (mg/dL)	164.00	155.74	0.2215
HDL-C (mg/dL)	42.00	48.82	0.0609
LDL-C (mg/dL)	89.43	85.42	0.3870
TG (mg/dL)	162.33	126.58	--
CK (UI/L)	119.66	145.80	--
AST (UI/L)	22.00	22.64	0.3729
ALT (UI/L)	18.66	19.08	0.4599

Note: $p \leq 0.05$ indicates statistically significant difference.

Table 3 - Unpaired t-test comparing atorvastatin users at standard dosage with higher dosages and biochemical exams, after at least seven months of treatment (CI, 95%), Recife, PE (n=95)

Parameters	Atorvastatin 10 mg (n=56)	Atorvastatin 20/40 mg (n=39)	p
Total cholesterol (mg/dL)	175.3	175.9	0.4686
HDL-C (mg/dL)	51.8	50.13	0.2621
LDL-C (mg/dL)	90.17	88.98	0.4149
TG (mg/dL)	156.1	190.89	0.0657
CK (UI/L)	131.26	138.5	0.3630
AST (UI/L)	23.81	23.0	0.3192
ALT (UI/L)	23.81	26.45	0.1074

Note: $p \leq 0.05$ indicates statistically significant difference.

2008), Scotland, Ireland and Netherlands (Shepherd *et al*., 2002), and with the Brazilian Cardiology Society in Brazil (Xavier *et al*., 2013).

Increased age (> 50 years) provides a greater risk for cardiovascular events (Brazil, 2013) and the elderly population (> 60 years) is high in Recife with approximately 940 thousand inhabitants (IBGE, 2010).

When the prescriptions for statins were analyzed, most patients used atorvastatin. The study shows that 54 (47.8%) were using statins in doses above the standard scales. According to Andrés & Zubicaray (2008), the reduction of cardiovascular events occurs with all statins, reducing 30-40% of LDL-C level with standard scales doses.

The present study shows that higher statin dosage use did not cause a statistically significant increase in the effectiveness profile, showing that the same effectiveness profiles can be obtained with a lower (standard) dosage use or higher doses. Therefore, the use of higher dosages with the intention of attaining better pharmacotherapeutic results would be unjustified.

In terms of effectiveness, the obtained results showed that statins were similarly effective, with very similar effectiveness frequencies: 38.9% (7 users) and 42.1% (40 users) for simvastatin and atorvastatin, respectively. Similar results were observed by Recto *et al*. (2000), in a previous study. An interesting result was that the simvastatin users presented lower total cholesterol and TG levels when compared to atorvastatin users ($p < 0.05$).

According to the study by Rocha Filho *et al*. (2013), atorvastatin has the higher cost of treatment per day, with a price range between 3,310% to 8,425% when compared to simvastatin. These results also corroborate with the analysis of Ministry of Health of Brazil in 2007, when he states that atorvastatin has a cost-effective very low in compared to simvastatin (Johannesson *et al*., 1997).

Interventions by cost-benefit analysis in prescriptions for statins can lead to significant changes in prescriptions, reduction in spending on pharmacotherapy and great savings for public coffers (Rocha Filho *et al*., 2013).

Some prescriptions have had as objective the achievement of therapeutic LDL-C levels of less than 70 mg/dL. However, no study testifies this benefit, and especially in preventing infarction in patients with high cardiovascular risk. It was found that these objectives are based on extrapolated data from randomized controlled study (Andrés & Zubicaray, 2008; Nelson *et al*., 2009). Finally, in order to achieve very low LDL-C values, high doses of statins are used, increasing the adverse effects risk.

The most frequent reason for ineffectiveness of treatment (66 patients) was LDL-C level above 100 mg/dL, followed by triglyceride levels above 200 mg/dL. An investigative study through pharmacotherapeutic follow-up methods (Cipolle *et al*., 2004; Dáder *et al*., 2007) is suggested in order to identify the causes that are interfering with the treatment effectiveness.

Studies in Brazil show that several factors may interfere with treatment effectiveness, such as the lack of

information on how to use the medicines correctly, drug interactions with food or other drugs, irresponsible self-medication, misunderstanding of instructions by users and the voluntary abstention of the patient to use prescribed medication (Souza *et al*., 2009; Carvalho *et al*., 2012; Bonadiman *et al*., 2012).

Recently, pharmaceutical care performed with patients with uncontrolled dyslipidemia significantly reduced the levels of atherogenic lipoproteins, as well as blood pressure, contributing to the improvement of life of the patients. These data are part of another study carried out in which serum presented a reduction of approximately 39% in LDL-C, triglycerides 44% and 25% of total cholesterol ($p < 0.05$) (Silva, *et al*., 2013).

In addition to the pharmacological treatment aspects of dyslipidemias, there are non-pharmacological therapeutic actions that directly influence treatment effectiveness, such as adequate diet, regular aerobic exercise and smoking abstention (Brazil, 2013).

Still, regarding the treatment effectiveness, HDL-C levels below 40 mg/dL after at least seven months of treatment was found in 26 users (39.4%). This data merits attention, because this lipid fraction is considered a cardiovascular protective factor that must be monitored in medical evaluations.

About the security aspects, no user had CK levels above 10 times the normal value described in the literature. However, 24 users had elevated total CK between 1-3 times the normal values. In cases of progressive elevations and levels above 3 times the normal total CK value, the monitoring and investigation of muscle pain symptoms and muscle or joint sensitivity are recommended (Brazil, 2013; Xavier *et al*., 2013).

In this study, more than half of the users who had high total CK levels, used doses above the standard scales, regardless of the type of statin. This result shows that all statins showed a similar safety profile for CK, with no significant statistical difference between the two medicines.

Liver transaminases levels elevation was found in 9.6% of users, and both enzyme levels were between 1-2 times the normal values. These values are higher than those recommended by the literature for statins use, for example, in 0.5% to 2% of cases, these being dose-dependent alterations (Farmer *et al*., 2002; Smith *et al*., 2003). This may be due to the use of other drugs, which is a very common event in the elderly population, which averages around 7 drugs per user (Loyola *et al*., 2005; Ribeiro *et al*., 2008; Souza *et al*., 2009).

Despite the increase in levels of transaminases, suspension or reduction of the statin dose should occur only when there is an increase of more than three times the normal value or when the elevation is persistent (FDA, 2000; Brazil, 2013).

Regarding the safety aspect, a higher dose of statins did not follow a statistically significant increase in the transaminase levels ($p > 0.05$), when compared to the same medicine in the standard dose.

When the two statins where compared, a statistically significant difference was observed in the ALT levels, showing that simvastatin use was related to a minor increase in the transaminase levels when compared to atorvastatin use, which showed a larger increase.

CONCLUSION

The present study showed that effectiveness and safety profiles in patients with dyslipidemia who use statin were not fully satisfactory. The results show a need for pharmacotherapeutic monitoring, as well as other studies with Evaluation of Results of Therapeutic Interventions and Cost-Benefit Analysis.

It was observed that higher simvastatin and atorvastatin doses showed no statistical difference in the reduction of lipid profile, suggesting that the same results can be obtained with a lower standardized dose. These data also support the use of simvastatin as the drug of choice for the treatment of dyslipidemias in the Brazil's Unified Health System, since it has better cost-benefit relation.

The study provided data that may be relevant to the discussion of the use statins and their therapeutic targets in patients with high cardiovascular risk and dyslipidemias. In the same way, may reflect in cities with health characteristics similar and lead to new strategies of government to improve the quality of life of patients.

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