Original Article

Evaluation of Sexual Dimorphism in the Efficacy and Safety of Simvastatin/Atorvastatin Therapy in a Southern Brazilian Cohort

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Abstract

Background: Dyslipidemia is the primary risk factor for cardiovascular disease, and statins have been effective in controlling lipid levels. Sex differences in the pharmacokinetics and pharmacodynamics of statins contribute to interindividual variations in drug efficacy and toxicity.

Objective: To evaluate the presence of sexual dimorphism in the efficacy and safety of simvastatin/atorvastatin treatment.

Methods: Lipid levels of 495 patients (331 women and 164 men) were measured at baseline and after 6 ± 3 months of simvastatin/atorvastatin treatment to assess the efficacy and safety profiles of both drugs.

Results: Women had higher baseline levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) compared with men ($p < 0.0001$). After treatment, women exhibited a greater decrease in plasma TC and LDL-C levels compared with men. After adjustment for covariates, baseline levels of TC and LDL-C influenced more than 30% of the efficacy of lipid-lowering therapy ($p < 0.001$), regardless of sex. Myalgia [with or without changes in creatine phosphokinase (CPK) levels] occurred more frequently in women (25.9%; $p = 0.002$), whereas an increase in CPK and/or abnormal liver function was more frequent in in men (17.9%; $p = 0.017$).

Conclusions: Our results show that baseline TC and LDL-C levels are the main predictors of simvastatin/atorvastatin therapy efficacy, regardless of sex. In addition, they suggest the presence of sexual dimorphism in the safety of simvastatin/atorvastatin. The effect of sex differences on receptors, transporter proteins, and gene expression pathways needs to be better evaluated and characterized to confirm these observations. (Arq Bras Cardiol. 2014; 103(1):33-40)

Keywords: Simvastatin; Atorvastatin; Sexual Dimorphism; Lipids.

Introduction

Dyslipidemia has been established as the primary risk factor for cardiovascular disease (CVD)[1]. Statins are a class of lipid-lowering drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, a key enzyme in the intracellular synthesis of cholesterol. Statins promote an increase in low-density lipoprotein cholesterol (LDL-C) receptors in hepatocytes, an increase in the removal of LDL-C particles from blood, and a decrease in total cholesterol (TC) and LDL-C levels[2].

In addition to their cardioprotective effects, statins also exhibit many pleiotropic effects, including anti-inflammatory and antioxidant properties[3]. Although statins are well tolerated by patients and have a good safety profile, some patients develop adverse drug reactions (ADRs) or do not show the desired pharmacological efficacy[4]. Simultaneous drug use with statins may increase the risk of ADRs due to drug–drug interactions[5].

Drug response may vary according to sexual dimorphism[6]. Differences in pharmacokinetics and pharmacodynamics between sexes contribute to interindividual variations in drug efficacy and toxicity[7]. Endogenous hormonal factors differ between men and women, and the hormonal effects and quantities change with age[6,8]. The incidence of CVD is lower in women during their reproductive period than in men of the same age[9]. The sex hormone estrogen (17β-estradiol) may contribute to the decreased incidence of cardiac diseases in females[10]. However, women in their postmenopausal period are more likely to develop CVD compared with men[8].

A recently published meta-analysis shows that the benefits of statins in primary and secondary CVD prevention did not differ between sexes[11]. However, of the 18 studies analyzed, only seven were related to the use of simvastatin/atorvastatin.

Moreover, this study did not provide data on sex differences in the safety and efficacy of statins[12]. Therefore, we highlight the importance of studies providing efficacy and safety data for lipid-lowering therapies, with focus on the role of sexual dimorphism and interaction with co-medications.

This study aimed to determine the effects of sexual dimorphism and interaction with co-medications on the efficacy and safety of simvastatin/atorvastatin therapy in a southern Brazilian cohort of European descent.

Methods

Patients

This open prospective cohort study included patients with hypercholesterolemia who were receiving lipid-lowering therapy with simvastatin/atorvastatin. The patients were of European descent, as ascertained by skin color and morphological characteristics, lived in Porto Alegre, Brazil, and were collected for convenience. The sample size was estimated by the standard deviation in LDL-C levels and the expected difference between men and women after considering the following values: power of 80%, significance level of 5%, difference between men and women of 5 percentage points, and a standard deviation of 18 mg/dL. Considering these data, the estimated sample size initially comprised 205 men and 205 women. Our initial screening included 658 patients. The exclusion criteria for this study were as follows: age < 20 years, triglyceride concentration ≥ 400 mg/dL, altered thyroid stimulating hormone levels, impaired hepatic or renal function, unstable or uncontrolled disease that influences lipid metabolism, and previous therapy with other lipid-lowering drugs. After application of these exclusion criteria, 495 patients were considered eligible (simvastatin/atorvastatin therapy use). Physical examination, clinical data, and clinical laboratory data were obtained by the physician. Biochemical evaluation was performed prior to statin (simvastatin/atorvastatin) therapy initiation and after 6 months of treatment for the evaluation of therapeutic efficacy. Statin therapy and dose administered were determined by the physician on the basis of clinical characteristics. The patients received other medications, including calcium channel blockers, diuretics, and antithrombotic agents, and did not alter their medication regimens throughout the study.

To assess the lipid-lowering efficacy, lipid levels were measured at baseline and after 6 ± 3 months of treatment. Totally, 162 patients who received treatment for at least a year (35 ± 22 months) without developing ADRs were designated as a control group. Patients who exhibited an ADR, regardless of the duration of statin treatment, were designated as the case group. ADRs were diagnosed by the physician when patients presented one or more events of myalgia with or without an increase in creatine phosphokinase (CPK) levels and impairment in liver function concomitant with statin therapy. Myalgia was defined as muscle pain with normal or increased serum CPK levels and changes in liver enzyme levels as confirmed by increased serum levels of alanine aminotransferase or aspartate aminotransferase. The presence of ADRs was evaluated on an average of every 3 months. Patients were not included in the ADR group when other unrelated conditions caused muscle pain, such as exercise-induced myalgia, arthritis, and viral myalgia.

This study was approved by the Federal University of Health Sciences of Porto Alegre Ethics Committee. All subjects who agreed to participate in this study gave their informed consent. Previous studies have already analyzed part of this sample[13-17]. Financial support was provided by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq - Brazil), REUNI/UFCSPA scholarship program, PROAP-CAPES, PRONEX-FAPERGS/CNPq, and PRONEN-FAPERGS/CNPq.

Biochemical analyses and benchmarks

Serum levels of TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs) were determined from peripheral blood obtained after 12 h of fasting using standard methods with commercial kits. LDL-C levels were assessed by Friedewald et al[18]. The percentage of patients with normalized lipid levels after therapy was assessed according to the following National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines[19] for primary prevention of CVD: TC < 200 mg/dL, LDL-C < 100 mg/dL, HDL-C > 60 mg/dL, and TG < 150 mg/dL.

Statistical analysis

Statistical analyses were performed using SPSS® software version 18.0 (Chicago, IL, USA). TG levels were *ln*-transformed to eliminate skewness in data, and untransformed values are shown. Analyses were conducted using the whole sample and stratified by sex. We created a standardized statin dosage variable to avoid differences in lipid-lowering efficacy. According to the findings of Kivistö et al[20], the daily doses of simvastatin were transformed to equivalent doses of atorvastatin at a ratio of 2:1. The mean percentage change in plasma lipid levels was obtained from the difference in pre-and post-treatment lipid levels, multiplied by 100, and divided by the pre-treatment level for each parameter. To analyze the association between sexual dimorphism and lipid-lowering treatment, the mean percentage change in plasma lipid levels was compared using the general linear model Type III sum of squares. Models were adjusted for age, smoking status, baseline lipid levels, prior CVD, controlled hypothyroidism, and antithrombotic use. Linear regression analysis was performed to assess differences in the dependence of variables on lipid-lowering efficacy. Continuous variables are presented as means ± standard deviations. A p-value of <0.05 was considered statistically significant. Student's *t*-test was performed to assess differences between continuous variables. Categorical variables were compared using chi-square tests (a two-sided p-value of < 0.05 was considered statistically significant) with Yates's correction. When appropriate, adjusted residual values (cell-by-cell analyses) and the power of the tests were assessed by WINPEPI [21].

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Results

Clinical characteristics of patients

We investigated 495 European descendants from southern Brazil who used simvastatin/atorvastatin lipid-lowering therapy. This population-based study comprised 331 (66.9%) women and 164 (33.1%) men; 85.1% participants were simvastatin users and 14.9% participants were atorvastatin users. The average treatment duration for women and men was approximately 6.4 ± 3.4 months and 6.1 ± 2.9 months ($p = 0.357$), respectively, with no difference between sexes. The standard dose of statins did not differ between women (10.3 ± 4.7 mg) and men (10.2 ± 4.3 mg; $p = 0.840$). Patients were aged between 25 and 82 years (61 ± 11 years). The mean age of the female patients (62.3 ± 10.7 years) was higher than that of the male patients (59.9 ± 11.1 years; $p = 0.021$). The number of smokers was greater among men than among women ($p = 0.008$), while hypothyroidism was more frequent in women ($p < 0.0001$). The clinical and demographic characteristics of the sample are described in Table 1. In our study, women had higher mean baseline levels of TC, LDL-C, and HDL-C compared with men ($p < 0.0001$; Table 2).

Efficacy and safety of the lipid-lowering therapy and sexual dimorphism

During treatment, 96.5% patients achieved standard LDL-C levels, while 73.8% and 72.6% patients achieved the desired TC and TG levels, respectively. Analysis of HDL-C levels revealed that 85.5% men and 51.9% women achieved the recommended levels. A similar percentage of men and women exhibited normalized TC and LDL-C levels: 88.9% and 86.8%, respectively, for men and 88.5% and 87.2%, respectively, for women. Table 3 describes the mean percentage change in lipid levels with respect to sex. After 6 months of follow-up, women exhibited a greater decrease in plasma TC (-27.32 ± 12.51 vs. -24.57 ± 12.08; $p = 0.028$) and LDL-C ($-37.61 \pm 1\,8.34$ vs. -33.49 ± 7.38; $p = 0.014$) levels compared with men. After adjusting for covariates, baseline TC and LDL-C levels were the primary predictors of simvastatin/atorvastatin efficacy. After adjustment for covariates, baseline levels of TC and LDL-C influenced 35.8% and 36.3% of the efficacy of lipid-lowering therapy ($p < 0.001$), regardless of sex (Table 4).

When assessing the safety of simvastatin/atorvastatin therapy, we observed that 74 (14.9%) patients in the total sample developed ADRs. Myalgia (with or without an increase in CPK levels) occurred more frequently in women (25.9%; $p = 0.002$) than in men, whereas increased CPK levels and/or abnormal liver function developed more frequently in men (17.9%) than in women ($p = 0.017$; Table 5).

Interactions with co-medications

We analyzed the effects of the lipid-lowering therapies in the presence of other medications, including beta-blockers, antithrombotic agents, levothyroxines, diuretics, angiotensin enzyme converting inhibitors, calcium-channel blockers, vasodilators, nitrates, benzodiazepines, cytochrome (CYP) inhibitors, CYP substrates, and CYP inducers. Women who used calcium-channel blockers, diuretics, and antithrombotic agents exhibited a greater frequency of ADRs ($p = 0.014$, $p = 0.014$, $p = 0.002$; respectively).

The concomitant use of drugs affecting the lipid-lowering metabolic pathway, such as CYP3A4 inducers, substrates, and inhibitors, was assessed and showed no influence on the safety and efficacy of simvastatin/atorvastatin therapy. Likewise, analysis of other co-medications showed no influence on the simvastatin/atorvastatin therapy endpoint in this patient group.

Discussion

The objective of this study was to determine the effects of sexual dimorphism and interactions with co-medications on the efficacy and safety of simvastatin/atorvastatin therapy. High levels of TC, LDL-C, and TGs and low levels of HDL-C are significant predictors of atherosclerosis and CVD in all populations[22].

Analysis of the baseline lipid profile revealed that women had higher mean levels of TC and LDL-C compared with men. In addition, the average age was greater in women than in men in our study. The majority of women studied were post-menopausal and hormone-deficient. This condition leads to a worse lipid profile due to a decrease in estrogen production, resulting in downregulation of LDL receptors in the liver and, subsequently, decreased clearance of LDL-C from the serum[23].

During statin therapy, there is a decrease in LDL-C levels due to the hepatic inhibition of cholesterol synthesis, which leads to upregulation of LDL receptors and a clearance of LDL from the circulatory system[2]. Previous studies have shown that the percentage of men who achieve normal TC and LDL-C levels during statin therapy is significantly higher than that of women[24-25]. However, in our study, a similar percentage of men and women exhibited normalized TC and LDL-C levels.

3-hydroxy-3-methylglutaryl-coenzime A reductase is primarily expressed in hepatocytes, and the efficacy of statins is dependent on the local concentration of these drugs in the liver. In addition, individual differences in pharmacokinetics and pharmacodynamics contribute to interindividual variations that characterize drug responses[7]. An efficacy analysis of statin therapy revealed that the decrease in plasma TC and LDL-C levels was greater in females than in males. After adjustment for covariates, we observed that baseline TC and LDL-C levels were statistically significant covariates. Although several studies in the literature have shown differences in drug response between men and women, approximately 35%–40% of the efficacy of simvastatin/atorvastatin therapy was related to baseline lipid levels in each patient, regardless of sex. Statin therapy is more effective in subjects with higher TC and LDL-C levels. Sexual dimorphism is defined as differences in characteristics between men and women. Sexual dimorphism in humans is also associated with the prevalence, severity, and development of many common diseases such as autoimmune diseases[26], asthma[27], and cardiovascular disease[28], which may be due to differences

Table 1 – Patient characteristics

Characteristics	All	Women	Men	pª
Number	495	331 (66.9%)	164 (33.1%)	
Age (years)	61.5 ± 10.9	62.3 ± 10.7	59.9 ± 11.1	0.021
Statin Use (%)				0.229
Simvastatin	85.1	86.8	81.8	
Atorvastatin	14.9	13.2	18.2	
Treatment time (months)	6.3 ± 3.2	6.4 ± 3.4	6.1 ± 2.9	0.357
Standard dose (mg)	10.2 ± 4.6	10.3 ± 4.7	10.2 ± 4.3	0.840
Postmenopausal (%)		76.0		
Hormone therapy use (%)		14.1		
Smoking (%)				0.020
Past	12.1	8.9	18.2	
Current	8.7	8.1	9.8	
Never	78.5	82.8	71.2	
Prior CVD (%)	32.5	28.8	40.0	0.014
CVD Family history (%)	17.7	16.7	19.7	0.578
Glucose (mg/dL)	100.2 ± 23.9	99.8 ± 26.1	100.9 ± 19.3	0.658
Diabetes (%)	18.7	17.4	21.2	0.465
Hypertension (%)	71.3	71.3	71.2	1.000
Controlled hypothyroidism (%)	15.1	20.5	4.5	< 0.001
Concomitant therapy use (%)				
calcium channel blockers	17.9	16.3	21.3	0.165
Diuretics	39.5	42.0	34.7	0.126
Antithrombotic	26.6	23.8	32.3	0.039
CYP3A4 substrates	17.6	16.6	19.5	0.362
CYP3A4 inducers	1.6	1.5	1.8	0.719
CYP3A4 inhibitors	21.6	20.2	24.4	0.228

Values for age, treatment duration, standard dose, and glucose levels are expressed as means ± standard deviations; ªp-values represent differences between women and men; CVD: Cardiovascular disease.

Table 2 – Pretreatment lipid levels according to sex

	All (n = 495)	Women (n = 331)	Men (n = 164)	pª
TC (mg/dL)	247.3 ± 39.9	254.1 ± 39.5	234.2 ± 37.5	< 0.0001
LDL-C(mg/dL)	164.4 ± 35.6	169.1 ± 34.9	154.9 ± 36.3	< 0.0001
HDL-C (mg/dL)	51.1 ± 12.8	54.0 ± 13.0	46.2 ± 11.0	< 0.0001
TG (mg/dL)ᵇ	157.7 ± 78.6	154.2 ± 68.3	164.8 ± 96.3	0.384

Values are means ± standard deviations; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; ªStudent's t-test for differences between woman and men; ᵇTG values were ln-transformed for comparisons.

Table 3 – Mean percentage changes in lipid levels according to sex

	All (n = 495)	Women (n = 331)	Men (n = 164)	p[a]	p[b]
TC (%)	-26.40 ± 12.42	-27.32 ± 12.51	-24.57 ± 12.08	0.028	0.406
LDL-C (%)	-36.41 ± 17.93	-37.90 ± 17.82	-33.41 ± 17.84	0.014	0.179
HDL-C (%)	3.68 ± 21.95	2.90 ± 21.11	5.25 ± 23.55	0.291	0.713
TGs (%)	-11.95 ± 32.14	-12.56 ± 31.56	-10.72 ± 33.36	0.572	0.328

Values are means ± standard deviations; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TGs: triglycerides; [a]Student's t-test for comparison between woman and men; [b] covariates included in the model: age, smoking status, baseline lipid levels, prior CVD, controlled hypothyroidism, and antithrombotic use.

Table 4 – Linear regression analysis: factors associated with percentage change in TC and LDL-C levels

Covariates	Regression coefficient ± standard error	Partial $R^2 \times 100$	p
TC			
Constant	1.742 ± 5.594		0.756
Age	0.009 ± 0.057	0.8	0.868
Gender	1.073 ± 1.290	3.8	0.406
Smoking	0.697 ± 0.817	3.9	0.394
Previous CVD	-0.276 ± 1.318	-0.9	0.834
Baseline TC levels	-0.117 ± 0.015	-35.8	< 0.001
Controlled hypothyroidism	1.324 ± 1.648	3.6	0.422
Antitrombothic use	-1.305 ± 1.393	-4.2	0.350
LDL-C			
Constant	0.988 ± 7.164		0.890
Age	-0.100 ± 0.083	-5.5	0.228
Sex	2.521 ± 1.872	6.2	0.179
Smoking	0.833 ± 1.209	3.2	0.491
Previous CVD	-1.729 ± 1.930	-4.1	0.371
Baseline LDL-C	-0.192 ± 0.024	-36.3	< 0.001
Controlled hypothyroidism	1.380 ± 2.411	2.6	0.567
Antitrombothic use	-1.433 ± 2.029	-3.2	0.481

TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; CVD: cardiovascular disease.

Table 5 – Adverse Drug Reactions (ADRs) according to sex

	All (n = 236)	Women (n = 158)	Men (n = 78)	p
Control	162 (68.6%)	105 (66.5%)	57[a] (73.1%)	
Myalgia (regardless of changes in CPK levels)	48 (20.3%)	41 (25.9%)	7[b] (9.0%)	0.002
Increased CPK and/or abnormal liver function	26 (11.1%)	12 (7.6%)	14[c] (17.9%)	

CPK: creatine phosphokinase; [a]Adjusted residual = 1.03, p = 0.302; [b]Adjusted residual = -3.05, p = 0.002; [c]Adjusted residual = 2.39, p = 0.017.

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in gene regulation between men and women. Previous studies have shown that sexual dimorphism affects mRNA expression[29-30]. Pilote et al[22] suggested the possibility that the evolution of sex differences in risk profiles can be partially attributed to sex hormones or their receptors. Previous studies have identified controversial data on differences in statin-induced responses between women and men[6,11-12,31-32]. Kostis et al[11] performed a meta-analysis to evaluate the effectiveness of statins in decreasing cardiovascular events in men and women. This study evaluated 18 randomized clinical trials of statin involving 141,235 participants in order to analyze sex-specific differences. They observed that the benefits of statins were similar between sexes, regardless of the type of control, baseline risk, or type of endpoint in primary and secondary prevention. Mosca[12] evaluated that study and stated that Kostis et al[11] did not provide data on statin efficacy with regard to sex-specific differences and safety. In addition, of the 18 trials evaluated by Kostis et al[11], only seven involved the use of simvastatin/atorvastatin. Therefore, we emphasize the importance of conducting cohort studies with a follow-up analysis to assess the efficacy of simvastatin/atorvastatin therapy.

Statin use can be associated with ADRs. In this study, we observed that myalgia (with or without an increase in CPK levels) occurred more frequently in women (25.9%; p = 0.002) than in men, whereas increased CPK levels and/or abnormal liver function was more commonly observed in men than in women (17.9%; p = 0.017). Studies have shown a difference in pharmacokinetics of up to 40% between men and women in terms of pharmacological response; furthermore, women have been shown to be at risk of clinically relevant ADRs[33]. Females have a higher percentage body fat compared with males, which can affect the drug distribution volume. A larger distribution volume will decrease the maximum concentration of the drug and increase its half-life and efficacy[33]. Genetic, physiological, and environmental effects can affect enzyme activity. Previous studies have shown that genetic polymorphisms promote variations in the expression of metabolizing enzymes, such as genes in the CYP 450 family, and are related to the efficacy and toxicity of statin therapy[34].

We also observed that women consuming calcium channel blockers, diuretics, and antithrombotic co-medications had a higher prevalence of ADRs compared with men. Although the pathogenesis of statin-related toxicity has been explained by multiple hypotheses, there is no clear consensus and uniform theory that can explain these effects[35].

Simvastatin and atorvastatin are metabolized by CYP 450 3A4 (simvastatin acid is also metabolized by CYP2C8). Exposure to CYP3A4 inhibitor drugs concomitantly with statins can lead to ADRs. Calcium channel blockers are potent CYP3A4 inhibitors at clinically relevant doses[36]. Kornstein et al[37] observed that the tolerability of antidepressant therapies is also sex-dependent. Other co-medications that were analyzed showed no influence on the simvastatin/atorvastatin therapy endpoint in this group of patients. However, an interaction between age and sex has also been demonstrated for a variety of CYP3A4 substrates[33]. The risk of ADR occurrence is 1.5–1.7-fold greater in women than in men[38]. Female sex, advanced age, presence of comorbidities, and use of concomitant medications were described as risk factors for statin-induced ADRs[39]. The Cholesterol Treatment Trialists' (CTT) Collaborators[40] published a systematic review of statin trials, suggesting strong evidence that the benefits of statin outweigh any possible serious ADRs. However, ADRs occurred in 14.9% patients in this study. Assessment of the cause of ADRs is important for optimizing the management of these subjects and the efficacy of lipid-lowering therapy.

The main strength of our study is that it is focused on the characteristics of patients receiving simvastatin/atorvastatin therapy as well as efficacy and safety profiles in a southern Brazilian cohort.

This study also has some limitations. It was an observational study with no placebo control. The sample was not equally distributed in terms of the baseline lipid profile, proportion of men and women, and age, and there was no age and sex matching. Some patients had incomplete data on hormonal status (women), hormone therapy use, genetic dyslipidemia, and lifestyle (diet and physical exercise). All patients were advised to begin physical activity and diet control, but monitoring and evaluation of these changes were not part of this work. Simvastatin/atorvastatin-induced ADRs were determined according to the physician's criteria and do not represent the incidence of ADRs in this population. In order to increase the power of the analysis, we collected patients who developed ADRs at some point during lipid-lowering therapy. Although the final sample size was different from the initially calculated sample size, our investigation displayed a power of 82% to detect differences of a five-percentage point decrease in LDL-C levels between men and women. We minimized the possibility of type II errors by using adjustment variables with covariates that could influence the final response.

Conclusions

In summary, we observed that simvastatin/atorvastatin therapy use was more effective in patients with higher TC and LDL-C levels, regardless of sex, and that ADRs were more frequent in women than in men. In the literature, we found a wide range of pharmacogenetic, pharmacokinetic, and pharmacodynamic statin-related studies. However, the role of sex differences in receptors, transporters proteins, and gene expression pathways needs to be better evaluated and characterized.

Author contributions

Conception and design of the research: Smiderle L, Almeida S, Hutz MH, Van der Sand CR, Van der Sand LC, Ferreira MEW, Pires RC, Fiegenbaum M; Acquisition of data: Smiderle L, Lima LO, Van der Sand CR, Van der Sand LC, Ferreira MEW, Pires RC; Analysis and interpretation of the data and Statistical analysis: Smiderle L, Almeida S, Fiegenbaum M; Obtaining financing: Almeida S, Fiegenbaum M; Writing of the manuscript: Smiderle L; Critical revision of the manuscript for intellectual content: Almeida S, Hutz MH, Fiegenbaum M.

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