Intermittent Doses of Statin in Hemodialysis Patients with Spontaneous Low LDL Cholesterol Levels

Paulo Giovanni de Albuquerque Suassuna and Marcus Gomes Bastos
Universidade Federal de Juiz de Fora - UFJF, Núcleo Interdisciplinar de Ensino e Pesquisa em Nefrologia - NIEPEN, Juiz de Fora, MG - Brazil

Summary

Background: Mortality in dialysis patients remains high and is due mainly to cardiovascular causes. Inflammation has a role in the genesis of accelerated atherosclerosis, vascular calcification, malnutrition and anemia, and a huge impact on the survival of these patients. The pleiotropic effects of statins can be a therapeutic option for reducing chronic inflammatory processes of patients undergoing hemodialysis.

Objective: To evaluate the effects of low doses of simvastatin on inflammatory markers, hematimetric and nutritional parameters of patients undergoing hemodialysis.

Methods: Clinically-stable patients undergoing hemodialysis were classified according to their baseline LDL-cholesterol levels in two groups: those with levels below 100mg/dl (Group 1) and those with levels equal to or greater than 100mg/dl (Group-2), and were treated with simvastatin during eight weeks. Group 1 received 20mg only after each session of hemodialysis (intermittent dose), whereas Group 2 received 20mg/daily. Laboratory data, erythropoietin resistance index and nutritional parameters were obtained before and after treatment.

Results: A significant and equivalent reduction in C-reactive protein levels in both groups was observed (35.97±49.23% *vs* 38.32±32.69%, p=0.86). In group 1, there was also a tendency towards reduced resistance to erythropoietin (228.6±16.2 *vs* 208.9±16.2, p=0.058) and improvement of hematimetric parameters (hematocrit: 33.1±5.9% *vs* 36.1±4.5%, p=0.021).

Conclusion: Intermittent doses proved to be as effective as the usual dose in reducing C-reactive protein levels and resistance to erythropoietin, besides improving the hematimetric parameters, indicating an important reduction of the cardiovascular risk evaluated by these parameters. (Arq Bras Cardiol 2008; 90(2):104-111)

Key words: Hydroxymethylglutaryl-CoA reductase inhibitors; renal dialysis; inflammation; C-reactive protein.

Introduction

Despite the improvement in dialysis techniques over the past few decades with the advent of proportioning and reverse osmosis units, mortality in patients undergoing the procedure is still very high, mainly due to cardiovascular causes[1]. Several studies have outlined the central role the hemodialysis-related chronic inflammatory process plays in accelerated atherosclerosis and cardiovascular mortality[2-5]. Moreover, inflammation in dialysis participates directly or indirectly in the pathophysiology of malnutrition, vascular calcification and cardiorenal anemia syndrome, with a huge impact on patient survival[6-8]. The causes of inflammation in dialysis are multifactorial; however, it has already been well documented that C-reactive protein (CRP) has a strong correlation with hypoalbuminemia, anemia, malnutrition and mortality, and is currently considered not only a marker, but also an important inflammatory mediator associated with endothelial dysfunction/activation and the pathogenesis of atherosclerosis[9-15].

Several observational studies on dialysis have already evidenced that statins play an important role in reducing all-cause and cardiovascular mortality, besides having an adequate safety profile, making them the first-choice treatment of dyslipidemia in dialysis[16-18]. Likewise, statins are also known for their ability to reduce the levels of CRP, and to simultaneously reduce the levels of CRP and LDL-cholesterol (LDL-c)[19,20]. For the population undergoing dialysis, however, definite evidence is lacking to prove the benefits of lowered cholesterol levels, and which would be the goals and the impact of reducing the chronic inflammatory process with the use of statins. Therefore, there is a gap in knowledge about the population undergoing dialysis, especially in the subpopulation affected simultaneously by low levels of LDL-c, high levels of CRP, hypoalbuminemia and refractory anemia. Mortality rates in this subpopulation are extremely high and there is no indication for the use of statins, since current guidelines are still based only on the serum levels of cholesterol[18].

The aim of this study is to evaluate the effects of intermittent doses of statins, targeting only their pleiotropic effects, on the inflammatory and nutritional markers of dialysis patients with spontaneous low levels of LDL-cholesterol.

Mailing Address: Paulo Giovanni de Albuquerque Suassuna •
Rua Dr. Jamil Altaf, 132 - Vale do Ipê - 36035-380, Juiz de Fora, MG - Brazil
E-mail: psuassuna@terra.com.br
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Methods

Study population and design

The study was conducted with all the clinically-stable patients enrolled in a hemodialysis program at the dialysis unit of the *Serviço de Nefrologia do Hospital Universitário da Universidade Federal de Juiz de Fora* (HU-UFJF) who met the following inclusion criteria: provided informed consent, were older than 18 years, were enrolled in the program for more than six months, had an arteriovenous fistula to allow access for hemodialysis, no clinical evidence of infectious processes in the previous three months, absence of neoplasms, autoimmune diseases and hepatitis, and no prior use of statins. The research project was reviewed and approved by the Institutional Review Board at UFJF.

Patients were divided into two groups: those with baseline LDL-c levels above 100 mg/dl and those below this value. This is the current cut-off level used for the formal indication of statins in the dialysis population[18]. The group of patients with spontaneously low LDL-c (below 100mg/dl) was named Group-1, whereas those with LDL-c equal to or greater than 100mg/dl constituted Group-2. Patients in Group-1 received the 20mg dose of simvastatin following the hemodialysis sessions, i.e., only three times per week (intermittent dose). This is a low dose aimed only at the pleiotropic effects and not a larger reduction in lipid levels. Patients in Group-2 received the usual 20mg/day dose of statin. The treatment was conducted with generic simvastatin (*Medley Indústria Farmacêutica SA*, São Paulo, Brazil), registered at *Agência Nacional de Vigilância Sanitária (ANVISA)*. Laboratory data were obtained, the erythropoietin resistance rate was calculated, and the malnutrition-inflammation score (MIS) was determined before and after the treatment. Treatment lasted for eight weeks, time known to be long enough to observe the effects of simvastatin on the lipid profile and CRP[9]. Patients excluded from the program were those who underwent transplantation, a change of technique or center, as well as patients who lost the hemodialysis access, developed infectious processes or neoplasms, were hospitalized, and those who chose to leave.

Dialysis adequacy

All patients underwent the dialysis sessions under the same conditions: use of polysulfone capillary dialyzer membrane (Hemoflow® F7 and F8, Fresenius Medical Care AG, Bad Homburg, Germany), bicarbonate bath (Farmarin, São Paulo, Brazil), and water treated by reverse osmosis (Permution, Curitiba, Brazil) according to guidelines set by ANVISA. All patients were submitted to three 4-hour sessions per week with the goal of achieving KT/V > 1.2 according to current guidelines set for hemodialysis adequacy[21].

Anemia management

Current guidelines for the treatment of anemia in chronic renal disease were followed[22]. All patients received erythropoietin (Hemax®, Biossintética, Brazil). The initial dose prescribed was 100ui/kg/week, adjusted as necessary in order to achieve hemoglobin levels between 11 and 13mg/dl and hematocrit between 33 and 39%. Likewise, all patients received intravenous iron (Noripurum®, Altana Pharma AG, Singen, Germany) to maintain transferrin saturation above 20% and ferritin >200ng/ml. Administration of intravenous iron was interrupted in the week preceding collection of laboratory data.

Laboratory data

Laboratory data are a part of the monthly routine tests performed on patients undergoing dialysis, as well as the measurement of ultrasensitive C-reactive protein (us-CRP). Blood was collected immediately before the first dialysis session of the week, since hemodialysis may induce elevation of CRP levels. Prior fasting could not be mandatory, as hemodialysis sessions were held at different times of the day. All tests were performed at the HU-UFJF laboratory, except for the measurement of us-CRP which was done at a certified commercial laboratory using serum from the same sample. Demographic and clinical data were obtained from the patients' medical records.

Levels of hemoglobin and hematocrit were determined with automated Cell-Dyn 3500R equipment (Abbott Laboratories, Illinois, USA). Concentrations of serum albumin and glutamic-pyruvic transaminase (GPT) were measured with the LabMax 240 device (Labtest Diagnóstica, Minas Gerais, Brazil) using the bromocresol green technique and the fixed-time kinetic method, respectively. Us-CRP was measured by immunoturbidimetry with the Cobas-Mira device (Roche Laboratories, Rotkreuz, Sweden) using an ultra sensitive CPR kit from BioTécnica (BioTécnica, Minas Gerais, Brazil), with a coefficient of variation of 4.15% and linearity up to 150mg/L. Lipid levels were obtained by a direct enzymatic method for measuring total cholesterol, HDL-cholesterol and triglycerides, and calculation of LDL-cholesterol (Friedewald formula).

Erythropoietin Resistance Index

The resistance to erythropoietin (EPO) is defined by the ratio EPOs/Hct, as described by GUNNELL J. et al[9], where EPOs represent the mean weekly EPO dose in the previous month and Hct, the mean hematocrit values during the previous two months. There is no adjustment for the patient's body weight, since the initial dose of erythropoietin is defined according to the weight, and dose adjustment depends on the patient's response with hematocrit elevation and treatment goals[9].

Malnutrition-Inflammation Score (MIS)

MIS - Malnutrition-Inflammation Score – is a quantitative method used to assess the presence and intensity of the malnutrition-inflammation syndrome (MIA-Syndrome), and it has been a useful tool both in determining the "clinical status" and in predicting the prognosis. This score uses the seven components of the Subjective Global Assessment of the nutritional status (SGA) incremented by three new elements: body mass index (BMI), serum albumin (Alb), and total iron-binding capacity as an indirect measurement of transferrin. The score has 10 components divided into four sections: nutritional history, physical examination, BMI and laboratory data. Each component has four levels of severity, scored from 0 (normal)

to 3 (very severe). The sum of scores ranges from zero to 30 points according to the level of severity. A MIS score of ≤8 indicates a normal nutritional status or mild malnutrition; a score of 9-18 indicates moderate malnutrition, and a score greater than 18, severe malnutrition. This score provides a correlation coefficient greater than isolated laboratory values and other scores such as SGA[23,24].

Statistical analysis

This is a prospective clinical assay conducted with two comparable groups of patients and an evaluation performed before and after treatment: Group-2 treated with a regular dose of statin and with formal indication of use, and Group-1 treated with alternative doses and indication. The Shapiro-Wilks test was used to assess the normality of the variables, and only us-CRP did not follow a normal distribution. Parametric variables are expressed as mean and standard deviation or percentage, when appropriate. Us-CRP is presented as median and range. The independent T-test or Mann-Whitney test was used for comparisons between the two treatment groups. To compare results of the same group before and after treatment, the paired T-test or Wilcoxon test was used. The correlation between demographic and laboratory variables was calculated using Pearson or Spearman correlations. A value of $p \leq 0.05$ was considered significant. SPSS 11.0 software was used to perform the statistical analysis.

Results

Of the 60 patients undergoing hemodialysis at HU-UFJF, 53 met the inclusion criteria and agreed to take part in the study. Of these 53, 11 patients were excluded from the study: three due to acute infectious processes; three left the program to undergo peritoneal dialysis and transplantation; two left due to loss of access; one was diagnosed with a neoplasm; one was hospitalized; and one dropped out of the program. No deaths occurred during the study.

Table 1 shows baseline demographic and laboratory data. Half of the patients were male. The most common etiology of chronic renal disease (CRD) was chronic glomerulonephritis (15 patients - 36%), followed by systemic arterial hypertension (10 patients - 24%). Only five patients were diabetic (12%), three of them belonging to Group-1.

All patients had been in the program for more than one year and, in general, showed good dialysis adequacy (Kt/V≥1.2), as well as adequate nutritional parameters (albumin and MIS). In general, hematimetric parameters were slightly below the target values and showed a moderate resistance to erythropoietin. The levels of us-CRP, maximum of 8.12mg/l, indicate that the selection of patients was successful, with no signs of activation of the acute-phase response. Also noteworthy was the mean level of LDL-c which was close to the goal of 100mg/dl.

When patients were divided into groups according to baseline LDL-c levels, 20 patients (47%) had LDL-c levels spontaneously lower than 100mg/dl (Group-1), whereas 22 had baseline levels greater than 100mg/dl (Group-2). In Group-1, the mean LDL-c measured was 77.5±16.4mg/dl, whereas in Group-2 it was 132.7±26mg/dl, with statistical distinction. Except for the levels of total cholesterol (TCL) and non-HDL cholesterol (NHDLC), the remaining variables did not differ between the groups and showed inter-group homogeneity (Table 2).

Comparing patients from Group-1 before and after the

Table 1 – Baseline demographic and laboratory data.

Variable	Minimum	Maximum	Average	SD
Age (years)	21	70	50.3	12.4
HD time (months)	12	175	77.7	46.7
Kt/V	0.93	1.91	1.37	0.29
MIS	1	14	5.7	2.9
Chol T (mg/dl)	104	289	171.2	42.9
LDL-c (mg/dl)	42	207	106.8	35.3
HDL-c (mg/dl)	14	61	36.7	9.8
nHDL-c (mg/dl)	79	256	135.1	41.6
TG (mg/dl)	51	260	153.4	54.7
BMI (Kg/m²)	15.36	28.53	21.9	3.47
Hb (g/dl)	7.8	13.9	10.8	1.6
Htc (%)	23	43.5	33.5	5.1
us-CRP (mg/l)	0.67	8.12	5.73*	-
EPO-RI	73.8	436.3	248.1	79.3
Alb (g/dl)	3.1	4.8	4.3	0.3

*Note: HD - Hemodialysis time; Kt/V - Dialysis adequacy index; CholT - Total cholesterol; LDL-c - Low-density lipoprotein; HDL-c - High-density-lipoprotein; nHDL-c - non-HDL cholesterol; TG - Triglycerides; BMI - Body Mass Index; Hb - Hemoglobin; Htc - Hematocrit; us-CRP - Ultra sensitive C-Reactive Protein; EPO-RI - Erythropoietin Resistance Index; MIS - Malnutrition-Inflammation Score; Alb - Serum albumin. *Median.*

Table 2 – Comparison between the groups

Variable	Group 1 (n=20)	Group 2 (n=22)	p
Age (years)	50.1±12.5	50.4±12.6	0.819
HD time (months)	77.8±42.9	77.5±50.9	0.981
Kt/V	1.34±0.33	1.40±0.25	0.498
Chol T (mg/dl)	143.1±22.4	195.8±38.7	<0.0001
LDL-c (mg/dl)	77.5±16.4	132.7±26.0	<0.0001
HDL-c (mg/dl)	36.8±10.2	36.7±9.8	0.982
nHDL-c (mg/dl)	106.5±19.3	158.8±37.8	<0.0001
TG (mg/dl)	142.1±57.5	162.8±52.1	0.284
BMI (kg/m²)	21.2±2.9	22.53±3.8	0.215
Hb (g/dl)	10.7±1.8	10.84±1.4	0.745
Htc (%)	33.1±5.9	33.79±4.4	0.667
us-CRP (mg/l)	5.73 (0.67 – 8.12)*	6.17 (1.04 – 7.85)*	0.69
EPO-RI	228.6±16.2	266.7±18.0	0.535
MIS	5.8±3.4	5.7±2.5	0.988
Alb (g/dl)	4.3±0.4	4.3±0.2	0.545

*Note: Values are expressed as mean±SD; P is significant if p <0.05; *Median (range); Group 1 - Patients with LDL<100mg/dl; Group 2 - Patients with LDL>100mg/dl; n - number of patients in each group; HD Time - Hemodialysis time; Kt/V - Dialysis adequacy index; Chol T - Total cholesterol; LDL-c - Low-density lipoprotein; HDL-c - High-density-lipoprotein; nHDL-c - non-HDL cholesterol; TG - Triglycerides; BMI - Body Mass Index; Hb - Hemoglobin; Htc - Hematocrit; us-CRP - Ultra sensitive C-Reactive Protein; EPO-RI - Eythropoietin Resistance Index; MIS - Malnutrition-Inflammation Score; Alb - Serum albumin.*

treatment with intermittent doses of simvastatin, there was a significant drop in the levels of LDL-c (16%) and in the levels of us-CRP (36%). On the other hand, an improvement was observed in hematimetric parameters, in addition to a tendency towards reduced resistance to erythropoietin (Table 3).

In Group-2, besides a significant reduction in baseline LDL-c (37%), a drop was also observed in the other lipid parameters. There was an important reduction in us-CRP levels (38%). A reduction in erythropoietin resistance was also noted, whereas the hematimetric parameters remained stable. There was a significant decline in MIS scores. In this group, a significant reduction was once again observed in serum albumin levels as well as an increase in GPT levels (Table 4).

Table 3 – Results with the 20mg/post-HD dose (Group 1)

Variable	Baseline (n=20)	Treatment (n=20)	p
Chol T (mg/dl)	143.1±22.4	131.3±26.7	0.079
LDL-c (mg/dl)	77.5±16.4	64.0±16.88	0.001
HDL-c (mg/dl)	36.8±10.2	39.1±14.3	0.638
nHDL-c (mg/dl)	106.5±19.3	93.9±25.4	0.116
TG (mg/dl)	142.1±57.5	138.5±78.9	0.981
Hb (g/dl)	10.7±1.8	11.6±1.5	0.018
Htc (%)	33.1±5.9	36.1±4.5	0.021
us-CRP (mg/l)	5.73 (0.67 – 8.12)*	2.40 (0.40 – 6.90)*	0.022
EPO-RI	228.6±16.2	208.9±16.2	0.058
MIS	5.6±3.4	5.2±2.5	0.59
Alb (g/dl)	4.3±0.4	4.1±0.4	0.15
GPT (mg/dl)	19.3±8.9	21.8±9.3	0.12

*Note: Values are expressed as mean±SD; P is significant if p <0.05; *Median (range); Chol T - Total cholesterol; LDL-c - Low-density lipoprotein; HDL-c - High-density-lipoprotein; nHDL-c - non-HDL cholesterol; TG - Triglycerides; Hb - Hemoglobin; Htc - Hematocrit; us-CRP - Ultra sensitive C-Reactive Protein; EPO-RI - Erythropoietin Resistance Index; MIS - Malnutrition-Inflammation Index; Alb - Serum albumin; GPT - Glutamic pyruvic transaminase; (N) - Number of patients.*

When the cardiovascular risk is stratified according to the serum levels of us-CRP, it is clear that, before treatment, 76% of the patients of both groups presented serum us-CRP levels greater than 3.0mg/l, which, according to the American Heart Association, characterizes high cardiovascular risk for the overall population[25]. After treatment, this percentage dropped to 57%. When the analysis is performed separately for each group, in Group-1 serum us-CRP dropped from 70% to 30%, whereas in Group-2, the decline was smaller, from 81.8% to 54.5% (Table 5).

By dividing patients according to the levels of us-CRP (lower or higher than 5.1mg/L), which is the brazilian cut-off value for the dialysis population[26], we observed that, except for LDL-c, the treatment with simvastatin had a significant impact only on those patients with baseline us-CRP levels higher than 5.1mg/L. For these patients, besides the drop in us-CRP and LDL-c levels, there was also a reduction of resistance to erythropoietin and an elevation of hematimetric parameters (Table 6).

The correlation between demographic and nutritional data with baseline laboratory parameters showed that us-CRP correlated with lower levels of hemoglobin and hematocrit (R=-0.31, p=0.04; R=-0.30, p=0.05) and indicated a greater resistance to erythropoietin (R=0.30, p=0.075).

Discussion

This was the first study conducted to evaluate the effect of an intermittent dose of simvastatin on the serum levels of us-CRP, hematimetric parameters, resistance to erythropoietin and nutritional parameters in patients undergoing hemodialysis who had LDL-c levels spontaneously lower than 100mg/dl. Moreover, the effects found in this group were compared to those found in a similar group of patients, but with a formal indication for statin use based on their serum LDL-c levels. The intermittent dose of statin was used because of the lack of definite evidence of the benefits of using statins in dialysis, especially in patients with LDL-c levels spontaneously lower than 100mg/dl. Therefore, this was an exploratory dose aiming just for the pleiotropic effects of statins, chiefly the anti-inflammatory effect.

In this study, we sought to select a population of hemodialysis patients who were clinically stable, with no evidence of acute inflammatory or infectious processes and who were undergoing dialysis under the same conditions; we also followed current guidelines on dialysis adequacy and anemia management. Our intent was, therefore, to homogenize as much as possible the study population and restrict possible external causes of an inflammatory process. The success of the approach is shown by an average of 5.39±2.24mg/L in us-CRP levels, as well as by the absence of levels higher than 10mg/L which would suggest an acute-phase response in hemodialysis. Likewise, no severe anemia or malnutrition was observed.

By dividing the population according to their levels of LDL-c, two population sets were found to have very similar characteristics. As mentioned above, 47% of the patients had baseline LDL-c levels spontaneously lower than 100mg/dl and high mean us-CRP levels, although this did not imply the presence of MIA-Syndrome[6] as these patients had normal nutritional parameters. This finding shows that the frequently low levels of LDL-c in the dialysis population do not affect exclusively malnourished patients or those affected by macroinflammatory processes, but are a characteristic of this population[27]. It is known that the lipid profile of hemodialysis

Table 4 – Results with the 20mg dose (GROUP 2)

Variable	Baseline (N=22)	Treatment (N=22)	P
Chol T (mg/dl)	195.8±38.7	138.9±26.4	<0.0001
LDL-c (mg/dl)	132.7±26.0	82.59±21.86	<0.0001
HDL-c (mg/dl)	36.7±9.8	39.2±6.2	0.027
nHDL-c (mg/dl)	158.8±37.8	99.6±24.0	<0.0001
TG (mg/dl)	162.8±52.1	133.2±48.2	<0.0001
Hb (g/dl)	10.8±1.4	11.1±1.4	0.237
Htc (%)	33.8±4.4	34.9±4.2	0.126
Us-CRP (mg/l)	6.17 (1.04 – 7.85)*	3.75 (0.20 – 7.20)*	<0.0001
EPO-RI	266.7±18.0	212.3±17.4	0.001
MIS	5.7±2.5	4.62±2.7	0.022
Alb (g/dl)	4.3±0.2	4.1±0.2	0.005
GPT (mg/dl)	16.2±6.4	19.4±8.8	0.037

*Note: Values are expressed as mean±SD; P is significant if p <0.05; *Median (range); Chol T - total cholesterol; LDL-c - low-density lipoprotein; HDL-c - high-density-lipoprotein; nHDL-c - non-HDL cholesterol; TG - triglycerides; Hb - hemoglobin; Htc - hematocrit; us-CRP - ultra sensitive C-Reactive Protein; EPO-RI - Erythropoietin Resistance Index; MIS - Malnutrition-Inflammation Index; Alb - serum albumin; GPT - glutamic pyruvic aminotransferase; (N) - number of patients.*

Table 5 – Distribution of patients before and after treatment, according to serum levels of us-CRP (Cardiovascular risk stratification – American Heart Association)

Group 1 (20mg post-HD)			Group 2 (20mg per day)		
us-CRP (mg/l)	Pre N (%)	Post N (%)	us-CRP (mg/l)	Pre N (%)	Post N (%)
>3.0	14(70%)	6(30%)	>3.0	18(81.8%)	12(54.4%)
3.0-1.0	5(25%)	10(50%)	3.0-1.0	4(18.2%)	4(18.2%)
<1.0	1(5%)	4(20%)	<1.0	-	69(27.3%)

Note: Values are expressed as number of patients (%); us-CRP - Ultra sensitive C-Reactive Protein; Group 1 - patients with baseline LDL-c lower than 100mg/dl who received 20mg simvastatin after dialysis; Group 2 - patients with baseline LDL-c higher than 100mg/dl who received 20mg/day of simvastatin.

Tabela 6 – Effect of simvastatin on patients with us-CRP lower or higher than 5.0mg/L

Range	us-CRP < 5.1mg/l			us-CRP >5.1mg/l		
	Before	After	P	Before	After	P
us-CRP (mg/l)	2.7(0.7-4.8)	0.9(0.2-6.9)	0.249	6.7(5.5-8.1)	4.5(0.4-7.2)	<0.0001
LDL-c (mg/dl)	97.3±44.9	71.0±27.6	0.001	111.7±29.6	75.5±18.1	<0.0001
EPO-RI	213.9±75.2	210.8±76.8	0.852	267.8±76.0	210.4±76.0	<0.0001
Hb (g/dl)	11.4±1.8	11.4±1.4	0.964	10.4±1.3	11.3±1.4	0.002
Htc (%)	35±5	35±4	0.850	32±4	35±4	0.001

Note: Values are expressed as mean±SD; P is significant if p <0.05; NS - non significant; LDL-c - low-density lipoprotein; Hb - hemoglobin; Htc - hematocrit; us-CRP - ultra sensitive C-Reactive Protein; EPO-RI - Erythropoietin Resistance Index.

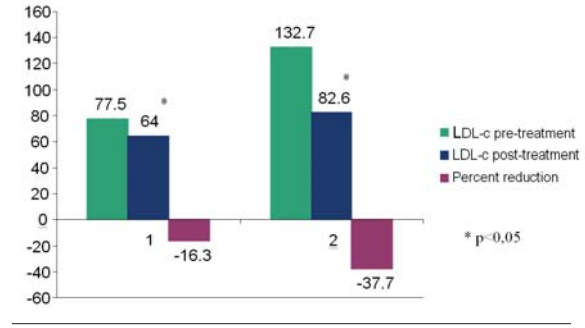
patients is different from that of the overall population and is characterized by very low levels of HDL-cholesterol and reduced ApoA-1 content, high levels of triglycerides and non-HDL cholesterol, and normal-to-low levels of total cholesterol and LDL-cholesterol[28]. However, this is a highly atherogenic profile due to the waste produced by degradation of LDL-cholesterol, with the presence of LDL-cholesterol and dense particles of LDL-cholesterol, and increased contents of ApoB and ApoC-III. These alterations likely occur due to the reduced activity of hepatic and peripheral lipases.

Thus, the serum levels of cholesterol in the dialysis population do not carry the same correlation with cardiovascular mortality shown by the overall population[29]. Despite such differences, current treatment guidelines for dyslipidemia in chronic renal disease still use goals set for the overall population due to the lack of studies involving populations undergoing dialysis.

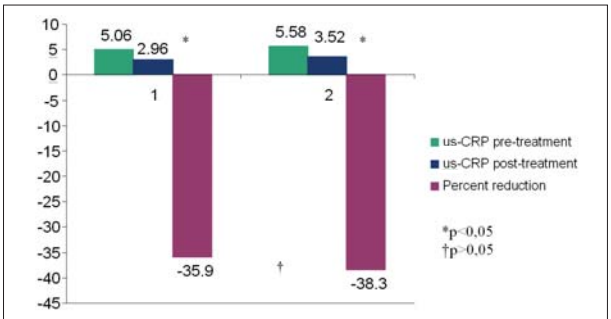
Chang et al[27] was the first to show a reduction in us-CRP levels with the use of simvastatin in hemodialysis. In his study, 62 patients undergoing dialysis with total cholesterol levels higher than 200mg/dl were randomized to receive simvastatin 20mg/day or placebo during eight weeks. A mean reduction of 41% was evident in the levels of LDL-c and 47% for us-CRP. It is worth mentioning that all patients received 20mg of simvastatin and had formal indications for the drug. In this study, the evaluation of Group-2 before and after treatment showed a significant reduction in LDL-c (28%) and in us-CRP (37%); these reductions were also very expressive from a clinical point of view. There was a drop in resistance to erythropoietin and an improvement in the hematimetric parameters, and the values reached were within the target range. The joint reduction in levels of us-CRP, LDL-c and resistance to erythropoietin with improvement of anemia point to a considerable drop in cardiovascular risk.

In Group-1, the low simvastatin dose, despite aiming only for the pleiotropic effects, was capable of significantly reducing the levels of LDL-c by 16%. Likewise, there was a 36% reduction in us-CRP levels and an elevation of hematimetric parameters, consequently reaching the goal. There was a tendency towards reduced resistance to erythropoietin which may be due to the small size of the sample. It is worth mentioning that 60% of the patients in this group achieved LDL-c levels lower than 70mg/dl which, in the overall population, would correspond to an alternative treatment target of dyslipidemia reserved for patients with known atherosclerotic disease. Despite the low levels of LDL-c achieved by this subgroup of patients, no adverse effects were observed, suggesting a tolerance similar to that in the overall population[20].

In comparing the groups, Group-2 had a greater reduction in LDL-c (37%), with 63% of the patients reaching the goal (16.26±17.51% *vs* 37.73±11.73%, p<0.0001), besides the reduction in the other lipid parameters, an effect with dose-dependent intensity similar to that found in the overall population[20]. As to the levels of us-CRP, there was a 38% reduction, equivalent to that observed in Group-1 (35.97±49.23% *vs* 38.32±32.69%, p=0.86), pointing to a dose-independent effect unrelated to the drop in LDL-cholesterol, which also coincides with data from the overall population[20] (figure 1 and 2).



Graphic 1 - Comparison of percent reduction of LDL-c after treatment in both groups.



Graphic 2 - Comparison of percent reduction of us-CRP after treatment in both groups.

In Group-2, a significant reduction was also observed in the resistance to erythropoietin in addition to an elevation of hematimetric parameters, which, despite not having reached statistical significance, was capable of placing values within the target range. The improvement in the resistance to erythropoietin without a significant improvement in the hematimetric values can be explained by a reduction in the weekly dose of erythropoietin needed to maintain the already adequate hematimetric levels.

As to nutritional parameters, there was no change in MIS or BMI scores (data not shown) except for Group-2 MIS, suggesting that the eight-week period is not sufficient for changes in these parameters to be noticed. There was, however, an unexpected 3.7% drop in serum albumin levels in Group-2. This reduction reached statistical significance probably due to the great homogeneity of the sample, though it is clinically non-significant since all patients maintained their albumin levels within the normal range. It is known that albumin is a negative acute-phase protein that correlates inversely with us-CRP levels. However, within the microinflammatory context, when there is no activation of the acute-phase response, a correlation may not be evident. A slight increase (14%) was also noticed in GPT levels, which is expected to occur during treatment with statins, though insufficient to cause any hepatic dysfunction that could justify the drop in serum albumin.

Based on the AHA stratification for cardiovascular risk, the intermittent dose of simvastatin reduced from 70% to 30% the

number of patients in the group of high cardiovascular risk. In Group-2, the reduction was smaller. This observation may indicate a greater positive impact on Group-1. On the other hand, when the cut-off value used for us-CRP was equal to 5.1mg/L, a positive impact was achieved only in the group of patients with higher us-CRP levels. In patients with a us-CRP greater than 5.1mg/L, besides the reduction in us-CRP and LDL-c levels, a significant reduction in the resistance to erythropoietin and improvement of the hematimetric parameters was observed. These data may suggest that, in the absence of other evident inflammatory factors, microinflammation plays an important role in the resistance to erythropoietin and in anemia in the dialysis population, predisposing patients to the cardiorenal anemia syndrome.

By correlating us-CRP with the other demographic and baseline laboratory parameters, a correlation with smaller hematimetric levels and increased resistance to erythropoietin was noted. These facts corroborate data in medical literature that show a strong influence of inflammation on erythropoiesis[9].

The small number of patients participating in the study is a limitation; nevertheless, it is worth mentioning that the intention here was to select a very homogeneous population, excluding inflammatory processes other than uremia and the hemodialysis treatment itself, which was achieved by adopting strict inclusion criteria.

The single us-CRP concentration measurement may not represent the patient's "inflammatory status", since the levels of us-CRP may vary a lot during a long period of observation. However, this was a short eight-week study conducted with stable patients and close clinical follow-up. This situation is very different from that observed in longer duration prospective studies designed to assess survival, in which close clinical follow-up is not feasible and a periodical measurement of CRP is indicated. On the other hand, despite the short period having been sufficient to show changes in the levels of us-CRP, LDL-c and hematimetric parameters, it was insufficient for changes in BMI and MIS to be noticed, as changes in both refer to body composition.

Conclusion

The use of intermittent doses of simvastatin proved to be capable of significantly reducing the levels of us-CRP in a short period of eight weeks in a fashion equivalent to that of the usual dose, besides improving hematimetric parameters and inducing a slight reduction in LDL-c levels. The drop in us-CRP levels suggests a reduction in the microinflammatory process, which, together with the improvement in hematimetric parameters, points to an important decrease in the cardiovascular risk for these patients. Therefore, small doses of simvastatin may represent a therapeutic option for patients undergoing hemodialysis who have spontaneous low levels of LDL-c, high levels of us-CRP, and anemia non-responsive to usual measures.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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