



Late response to rosuvastatin and statin-related myalgia due to *SLCO1B1*, *SLCO1B3*, *ABCB11*, and *CYP3A5* variants in a patient with Familial Hypercholesterolemia: a case report

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Abstract: Statins are the most widely used cholesterol-lowering drugs for cardiovascular diseases prevention. However, some patients are refractory to treatment, whereas others experience statin-related adverse events (SRAE). It has been increasingly important to identify pharmacogenetic biomarkers for predicting statin response and adverse events. This case report describes a female patient with familial hypercholesterolemia (FH) who showed late response to rosuvastatin and experienced myalgia on statin treatment. In the first visit (V1), the patient reported myalgia to rosuvastatin 40 mg, which was interrupted for a 6-week wash-out period. In V2, rosuvastatin 20 mg was reintroduced, but her lipid profile did not show any changes after 6 weeks (V3) (LDL-c: 402 vs. 407 mg/dL). Her lipid profile markedly improved after 12 weeks of treatment (V4) (LDL-c: 208 mg/dL), suggesting a late rosuvastatin response. Her adherence to treatment was similar in V1 and V3 and no drug interactions were detected. Pharmacogenetic analysis revealed that the patient carries low-activity variants in *SLCO1B1**1B and*5, *SLCO1B3* (rs4149117 and rs7311358), and *ABCB11* rs2287622, and the non-functional variant in *CYP3A5**3. The combined effect of variants in pharmacokinetics-related genes may have contributed to the late response to rosuvastatin and statin-related myalgia. Therefore, they should be considered when assessing a patient's response to statin treatment. To the best of our knowledge, this is the first report of a pharmacogenetic analysis on a case of late rosuvastatin response.

Keywords: Pharmacogenetics; precision medicine; familial hypercholesterolemia (FH); statins; myalgia

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Introduction

Familial hypercholesterolemia (FH) is a genetic metabolic disease that leads to increased high low-density lipoprotein (LDL) cholesterol, which is a risk factor for early atherosclerosis and cardiovascular diseases (1). FH is usually treated with high-dose statins, which are inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMGR), a key enzyme in cholesterol biosynthesis

pathway. Rosuvastatin is one of the most effective statins, probably due its hydrophilicity, that confers selectivity to hepatic cells, higher affinity to HMGR, and lower rates of statin-related adverse events (SRAE) compared to other statins. It is poorly metabolized by CYP2C9 and CYP2C19, while 72% of the non-metabolized molecules are excreted via biliary system. Therefore, rosuvastatin blood levels rely on the activity of membrane transporters, mainly of solute

carrier (SLC) and ATP-binding cassette (ABC) families, highly expressed in intestine, liver, and kidney (2).

Pharmacogenetic studies have shown that loss-of-function variants in genes encoding OATPs, such as *SLCO1B1*, *SLCO2B1*, and *SLCO1B3*, and ABCs have been associated with variability in low-density lipoprotein cholesterol (LDL-c) reduction and higher risk of SRAE (3). The importance of considering the combined effect of variants in key genes for pharmacogenetic analyses has been increasingly evident (4). In this case report, we discuss how variants in genes participating in different stages of statin pharmacokinetics pathway possibly affected the time to response to rosuvastatin and the risk of SRAE in a female FH patient. To the best of our knowledge, this is the first report of a pharmacogenetic analysis on a case of late rosuvastatin response. This case is reported in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-5540>).

Case presentation

A 26-year-old Caucasian female patient with definite diagnosis of FH according to Dutch Lipid Clinic Network MEDPED criteria (5) was invited to participate in an intervention study in June 2019. She was previously included in a FH sequencing study (May 2018), in which a panel of 84 genes involved in lipid homeostasis and drug metabolism was sequenced using exon-targeted gene sequencing (NGS). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for both studies.

The patient carries the variant *LDLR* rs28941776 (c.1646G>A, p.Gly549Asp), which has been associated with FH and is classified as pathogenic according to the American College of Medical Genetics (ACMG) guidelines (6).

Her clinical history included high levels of total cholesterol and LDL-c since childhood. In 2008, at the age of 15 years, she had an abnormal lipid profile even under a daily treatment with simvastatin 10 mg and ezetimibe 10 mg. Laboratory analyses showed a total cholesterol of 324 mg/dL, LDL-c 264 mg/dL, high-density lipoprotein cholesterol (HDL-c) 46 mg/dL, and triglycerides 71 mg/dL. In 2014, she was diagnosed with hypothyroidism and treated with levothyroxine 25 µg/day,

which was gradually increased to 100 µg/day in 2019. She also had a pregnancy history in January 2017.

Her therapy history included simvastatin, which led to severe myopathy in 2008, with marked increase in serum creatine kinase (CK) to 1,080 U/L (4.7-fold the upper reference value). The cholesterol-lowering therapy was changed to pravastatin 20 mg and ezetimibe 10 mg daily until May 2011, when she reported another episode of myalgia. Pravastatin was withdrawn and atorvastatin 20 mg was introduced, also associated with ezetimibe 10 mg. Three months later, in August 2011, she reported interrupting atorvastatin treatment due to myalgia. Rosuvastatin 10 mg was then introduced, also associated with ezetimibe 10 mg, after which she showed an LDL-c level of 125 mg/dL and never reported myalgia again. However, her lipid profile worsened throughout the years even under rosuvastatin treatment, with her LDL-c reaching 194 mg/dL with rosuvastatin 20 mg.

The patient had no history of liver or kidney impairment, HIV, coronary artery disease (CAD), diabetes, obesity, cardiovascular events, and did not smoke or drink. Her mother and grandmother had a history of FH, but not CAD or cardiovascular events, while her father had hypertension and type 2 diabetes.

In the intervention study, the patient was seen four times (V1 to V4) in 5 months, and clinical history and therapy data were obtained. The protocol consisted of a 6-week rosuvastatin wash-out period, after which rosuvastatin was reintroduced for additional 6 weeks, when treatment response was evaluated. Adherence to treatment was assessed in each timepoint using the translated and validated version of the Brief Medication Questionnaire (BMQ) (7) and blood samples were taken in each visit for laboratory testing.

The lipid profile during the follow-up is shown in *Figure 1*. In April 2019 (V1), the patient was taking rosuvastatin 40 mg, ezetimibe 10 mg, and levothyroxine 88 µg daily. She reported experiencing muscle pain after recently increasing rosuvastatin dose from 20 to 40 mg/day. Her lipid profile was altered (total cholesterol 376 mg/dL, LDL-c 263 mg/dL, HDL-c 67 mg/dL, triglycerides 234 mg/dL) without increase in CK levels. She reported being active, running 2 km 2–3 times a week, and had a healthy diet, eating more than five portions of vegetables daily. Her TSH and T4 levels were normal. Rosuvastatin 40 mg was then discontinued for wash-out, ezetimibe was maintained, and levothyroxine dose was increased to 100 µg/day.

In June 2019 (V2), after undergoing a 6-week

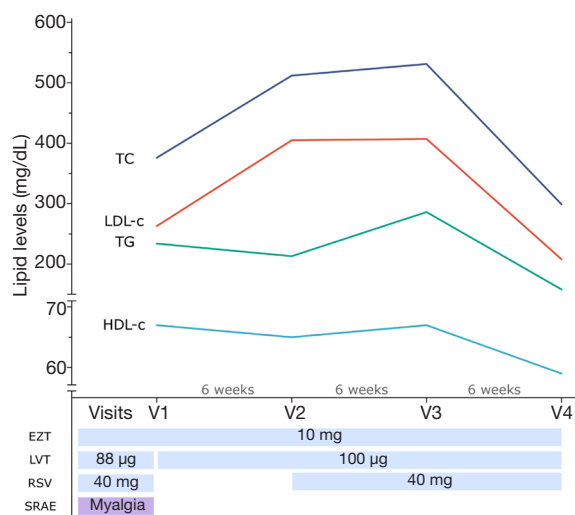


Figure 1 Plasma lipid profile and pharmacotherapy of the FH patient throughout the study period. EZT, ezetimibe; LVT, levothyroxine; RSV, rosuvastatin; SRAE, statin-related adverse events.

rosuvastatin wash-out period between V1 and V2, her lipid profile worsened (total cholesterol 512 mg/dL, LDL-c 405 mg/dL, HDL-c 65 mg/dL, triglycerides 213 mg/dL). Because the patient reported myalgia in V1 (rosuvastatin 40 mg), the physician prescribed rosuvastatin 20 mg/day for six weeks. Surprisingly, in August 2019 (V3), the lipid profile (total cholesterol 531 mg/dL, LDL-c 407 mg/dL, HDL-c 67 mg/dL, triglycerides 286 mg/dL) did not change compared to V2. The patient reported experiencing no myalgia to rosuvastatin 20 mg. In September 2019 (V4), her lipid profile improved (total cholesterol 299 mg/dL, LDL-c 208 mg/dL, HDL-c 59 mg/dL, triglycerides 158 mg/dL) and she continued not experiencing myalgia to rosuvastatin.

During the follow-up period, serum TSH and T4 levels remained unchanged, suggesting that her hypothyroidism was controlled and did not influence the lipid profile. Moreover, serum CK did not show any abnormality, which indicates no muscle damage due to statin treatment.

The patient also reported being adherent to treatment. In the BMQ adherence questionnaire, she reported forgetting the lipid-lowering medications 2 days in the week before V1 (71.4% adherence) and 1 day in the week before V3 (85.7% adherence).

The genetic profile of the patient is shown in *Table 1*. She carries five missense variants in *SLCO1B1*, *SLCO1B3*, and *ABCB11*. She is also homozygote for the *CYP3A5**3 (rs776746) splicing variant. No other missense variants

described as impacting rosuvastatin response were found in *CYP3A4*, *CYP2C9*, *CYP2C19*, or other drug transporters, such as *ABCG2* (data not shown).

Discussion

In heterozygous FH patients, LDL-c level reductions of 47.1% have been observed after a 6-week treatment with rosuvastatin 20 mg (8). The patient, however, did not experience any changes in LDL-c levels at week 6 (V3) of rosuvastatin 20 mg treatment, with a 48.9% LDL-c reduction only at week 12 (V4) of therapy.

The delayed rosuvastatin response could be explained by modifications in the therapy scheme during the follow-up period. However, the only change was in levothyroxine dose, that was increased from 88 to 100 µg in V1. It is unlikely that the late response is due to an adaptation to the new levothyroxine dose. The patient was already on treatment with levothyroxine 88 µg before V1; moreover, changes in cholesterol due to an adaptation period should be reflected in her lipid profile in V3, not only in V4. Another possible explanation is a lack of adherence from V2 to V3; however, the patient showed a similar treatment adherence in V3 and V1, which should lead to a similar lipid profile between visits. Furthermore, drug interactions between rosuvastatin, levothyroxine, and ezetimibe that could affect treatment response were not detected, excluding this possibility.

Pharmacokinetics-related genes may have contributed to the late response to rosuvastatin (*Figure 2*). The patient carries two variants in *SLCO1B1*, c.388A>G (*SLCO1B1**1B) and c.521T>C (*SLCO1B1**5), that are important determinants of rosuvastatin response. *SLCO1B1**5 is a loss-of-function variant that decreases the hepatic uptake and increases blood levels of statins (9) (*Table 1*). *SLCO1B1**1B has shown comparable activity to the functional *1A variant in *in vitro* functional studies (10). *SLCO1B1**1B and *5 variants are in linkage disequilibrium (LD) and form the *SLCO1B1**15 haplotype, that also reduced rosuvastatin uptake in functional studies with HEK293 and HeLa cells (11). The decreased liver uptake caused by these *SLCO1B1* variants has been associated with increased plasma levels of rosuvastatin in pharmacokinetics studies (9) (*Table 1*).

SLCO1B3 is also an important gene that encodes an influx transporter for rosuvastatin. The patient was homozygous for both *SLCO1B3* c.334T>G and c.699G>A, which are in strong LD (12). In an *in vitro* study, HeLa cells transfected with *SLCO1B3* c.334G and c.699A haplotype showed a 13% decrease in rosuvastatin uptake, while for

Table 1 Variants in pharmacokinetic-related genes of the FH patient with late response to rosuvastatin

Gene	Variant code	Variant type	Nucleotide change (Amino acid change)	Patient genotype	Allele frequency (1,000 genomes, %)	Functional impact	Effects on rosuvastatin pharmacokinetics	References
<i>SLCO1B1</i>	rs2306283 (<i>SLCO1B1*1B</i>)	Missense	c.388A>G (p.Asn130Asp)	AG	*1B: 54.4	Comparable to *1A	No effect on plasma rosuvastatin levels	Ho <i>et al.</i> , 2006; Lee <i>et al.</i> , 2013
<i>SLCO1B1</i>	rs4149056 (<i>SLCO1B1*5</i>)	Missense	c.521T>C (p.Val174Ala)	TC	*5: 8.8	Reduced activity	Increased rosuvastatin plasma levels; Reduced hepatic uptake	Kameyama <i>et al.</i> , 2005; Lee <i>et al.</i> , 2013
<i>SLCO1B1</i>	rs2306283, rs4149056 (<i>SLCO1B1*15</i>)	Missense	c.388A>G, c.521T>C (p.Asn130Asp, p.Val174Ala)	AG, TC	*15: 7.8	Reduced activity	Increased rosuvastatin plasma levels; reduced hepatic uptake	Kameyama <i>et al.</i> , 2005; Birmingham <i>et al.</i> , 2015
<i>SLCO1B3</i>	rs4149117	Missense	c.334T>G (p.Ser112Ala)	GG	G: 70.2	Reduced activity	Reduced hepatic uptake	Schwarz <i>et al.</i> 2011
<i>SLCO1B3</i>	rs7311358	Missense	c.699G>A (p.Met233Ile)	AA	A: 70.2	Reduced activity	Reduced hepatic uptake	Schwarz <i>et al.</i> 2011
<i>ABCB11</i>	rs2287622	Missense	c.1331T>C (p.Val444Ala)	TC	C: 58.9	Reduced activity	Increased rosuvastatin plasma levels	Soko <i>et al.</i> 2019
<i>CYP3A5</i>	rs776746 (<i>CYP3A5*3</i>)	Splicing	c. 6986A>G	GG	*3: 62.1	No activity	No rosuvastatin metabolism; Reduced LDL-c response	Bailey <i>et al.</i> 2010

FH, familial hypercholesterolemia; LDL-c, low-density lipoprotein cholesterol.

other substrates, such as cholecystokinin-8, an even more marked decrease of 57% was observed (13) (*Table 1*).

Although the effect of *SLCO1B3* c.334G and c.699A haplotype in rosuvastatin uptake is not sufficient to explain the delayed response, it might be significant when combined with the effect of the decreased function haplotype *SLCO1B1*15*. While *SLCO1B1*5* and *SLCO1B1*15* are associated with higher plasma levels of rosuvastatin, previous studies failed to find an association between these variants and LDL-c reduction in response to short- and long-term rosuvastatin treatments (9). Therefore, the simultaneous presence of decreased function *SLCO1B1* and *SLCO1B3* haplotypes possibly caused a marked reduction of rosuvastatin intrahepatic concentration, resulting in the lack of response observed in V3.

ABCB11 encodes the efflux protein ABCB11, which plays an important role in rosuvastatin bile excretion. In a recent study, *ABCB11* c.1331C allele has been associated to increased plasma rosuvastatin levels in healthy subjects (14) (*Table 1*). This variant possibly causes lower rosuvastatin excretion via bile, which in turn would increase intrahepatic rosuvastatin concentrations. Therefore, this mechanism could explain why even in the presence of low function SLC variants, the patient showed a late but evident LDL-c

reduction after 12 weeks of rosuvastatin treatment.

The patient also carries the homozygous form of *CYP3A5*3*, an intronic variant that results in undetectable expression of *CYP3A5* (15). The GEOSTAT-1 study reported that dyslipidemic patients carrying *CYP3A5*3*3* had lower LDL-c reduction after three-month rosuvastatin 10 mg treatment compared to carriers of *1/*1 or *1/*3 (*Table 1*). It was suggested that the metabolite produced by *CYP3A5* also plays a role in HMGR inhibition, potentiating the response to rosuvastatin, which is why *CYP3A5* non-expressors have reduced LDL-c response to rosuvastatin (16). *CYP3A5*3* possibly impaired the patient's response time to rosuvastatin, but in lower extent, as *CYP3A5* does not participate markedly in rosuvastatin metabolism.

In addition to the delayed response to rosuvastatin, the patient experienced myalgia associated with rosuvastatin 40 mg/day and other statins, as previously commented. This SRAE may be due to *SLCO1B1* variants. *SLCO1B1*5* and *SLCO1B1*15* have been extensively associated with myopathy to simvastatin. A systematic review and meta-analysis reported that carriers of the C allele of *SLCO1B1*5* (c.521T>C) showed a higher risk of myotoxicity (17). Additionally, *SLCO1B1*5* has been associated to rosuvastatin myotoxicity in previous studies (18,19). It has been

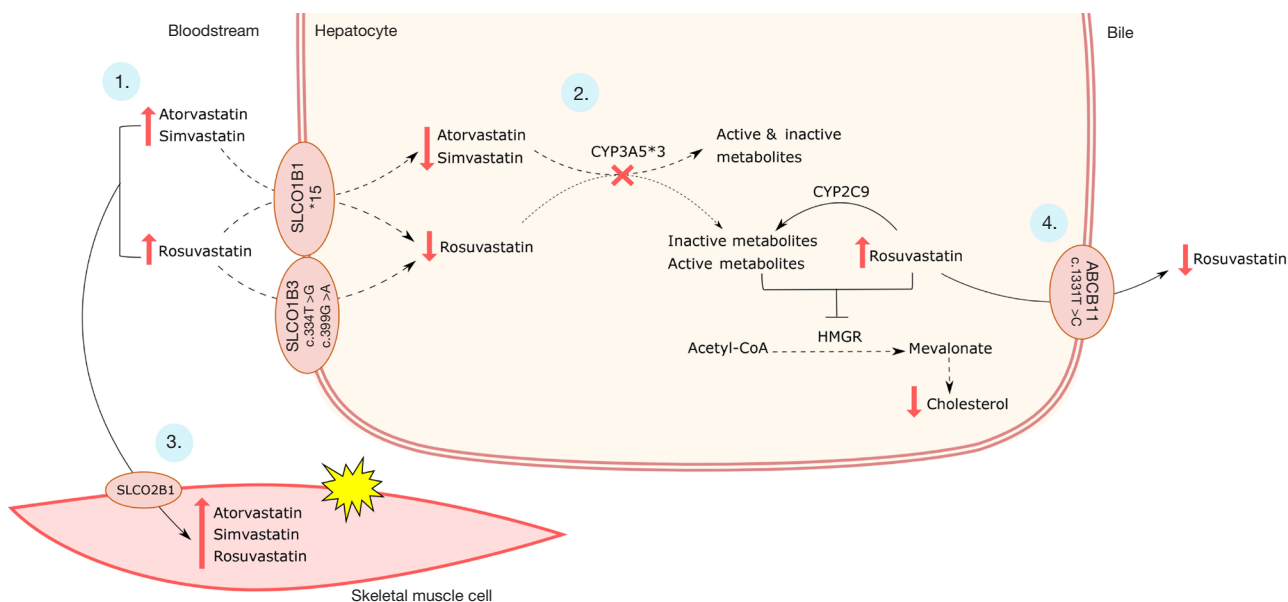


Figure 2 Proposed mechanism for patient's late rosuvastatin response and myalgia. 1. The hepatic uptake of rosuvastatin occurs through *SLCO1B1* and *SLCO1B3* influx transporters, while atorvastatin and simvastatin are internalized through *SLCO1B1*. The presence of deleterious variants in these transporters (*SLCO1B1**15 and *SLCO1B3* c.334T>G and c.699G>A) decreases statin uptake, therefore decreasing their concentration inside the hepatocyte and increasing statin plasma levels. 2. The lack of expression of *CYP3A5* due to *CYP3A5**3 also decreases atorvastatin and simvastatin metabolism, which contributes to increasing their plasma levels. This enzyme does not participate markedly in rosuvastatin metabolism. 3. The resulting higher blood statin levels increased the patient's muscular exposure to statins, that are internalized through *SLCO2B1* transporter into the skeletal muscle cell. The high concentrations in the skeletal muscle cell possibly caused patient's myalgia. 4. Rosuvastatin's bile excretion occurs through *ABCB11* efflux protein. *ABCB11* c.1331T>C variant results in a reduced activity *ABCB11*, which decreases rosuvastatin efflux; this increases rosuvastatin intrahepatic levels and blood levels. Although the patient had reduced function influx transporters, we suggest that the small portion of rosuvastatin absorbed in the beginning of the treatment accumulated due to the loss of function of the *ABCB11* variant. This, together with rosuvastatin active metabolites generated by the normal function *CYP2C9*, allowed *HMGCR* inhibition and therefore cholesterol lowering in the last visit.

suggested that it causes higher efflux of statins, increasing statin exposure and, therefore, the risk of myalgia (20). Also, a recent case report showed that variants in *SLCO1B3* (c.334T>G and c.699G>A) and *ABCB11* (c.1331T>C) and the interaction between rosuvastatin and ticagrelor led to rhabdomyolysis in a patient with chronic kidney disease and other chronic conditions (21), but no other reports were found.

*CYP3A5**3 may also have contributed to statin myotoxicity, since it has been associated with increased risk to atorvastatin and rosuvastatin-related myalgia in South-Indian dyslipidemic patients (22). However, this variant was not associated to statin intolerance in another study (23). Most studies have evaluated the effect of individual variants in *SRAE*, and not the interaction between a group of variants in key genes in statin pharmacokinetics pathway.

Therefore, we suggest that the combined effect of the low-activity variants in *SLCO1B1* and *SLCO1B3*, the high-activity variant in *ABCB11*, and the lack of activity of *CYP3A5**3 predisposed the patient to low hepatic uptake, metabolism and efflux, respectively. The resulting higher rosuvastatin plasma concentration increased its systemic exposure, which may have caused myalgia (Figure 2).

Importantly, the patient carries *LDLR* rs28941776 (c.1646G>A, p.Gly549Asp), a disruptive-missense variant that showed reduced LDL uptake in an *in vitro* study (24). *LDLR* variants have been associated with variability in statin response in FH patients (25), but we did not find studies that investigated the association between *LDLR* variants and time to statin response or myalgia. Nevertheless, this variant could have played a role in patient's rosuvastatin time to response and it should be considered for further

studies.

A limitation of this study is that plasma concentrations of rosuvastatin and its metabolites were not measured. However, the adherence of the patient to the prescribed treatment was ensured using a validated adherence questionnaire and regular follow-up calls.

In summary, the combination of four low-activity variants in *SLC* genes, a high-activity variant in *ABCB11*, and a non-functional variant in *CYP3A5* may explain the observed late response to rosuvastatin and the statin-related myalgia. With this case report, we have shown the importance of considering a combination of variants in a pharmacogenetic analysis to predict individual responses to statin treatment and prevent adverse drug events. We believe this study contributes to precision medicine in future clinical settings.

Patient perspective

“I have had high cholesterol since I was a child and it has been an issue because of the delayed response to treatments and of many adverse reactions to medications, especially simvastatin. The authors have been very attentive towards me throughout the whole study and discovered possible variants that may delay my response to rosuvastatin and influence the pain that I have felt when using statins. I am very happy for knowing the cause of my problem and I would like to thank the authors for this possible diagnosis. This has improved my perspectives of cholesterol treatment.”

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-5540>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The intervention study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The DNA sequencing study was approved by the Ethics Committees of the Institute Dante Pazzanese of Cardiology (CAAE #4618713.0.1001.5462) and the School of Pharmaceutical Sciences of the University of Sao Paulo (CAAE #24618713.0.3001.0067), Sao Paulo, Brazil. The intervention study was approved by the Ethics Committee of the Institute Dante Pazzanese of Cardiology (CAAE #05234918.4.0000.5462). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committees. The patient signed the written informed consents before her enrollment in the studies. In the written informed consent of the DNA sequencing study, the patient was informed that clinical data and blood samples would be collected for laboratory tests and genetic analyses. As for the intervention study, the patient was informed on the intervention protocol and sample collections throughout the visits, and that this data would be used for genetic and epigenetic analyses.

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