Peer Review File

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Responses to Review Comments

Comment 1:

This case report shows that a patient with familial hypercholesterolemia harboring variants in the SLCO1B1, SLCO1B3, ABCB11, and CYP3A5 genes had late response to rosuvastatin and statin-related myalgia. The reviewer wonders if these genetic variants really contribute to the phenotype of late response to rosuvastatin and statin-related myalgia of the patient. [The proband had a pathogenic variant In the LDLR gene, so the effect of LDLR pathogenic variant on late response to rosuvastatin should be considered.

Reply: We would like to thank the reviewer for the discerning review and the valuable contribution that helped to improve our manuscript.

Indeed, the *LDLR* pathogenic variant should be considered as an additional factor for the late response to rosuvastatin. To the best of our knowledge, no studies were published associating this variant to the variability in time to response to statin or to myalgia, but only to a lower percentage of LDL-c reduction in *LDLR* pathogenic carrier variants. We therefore included a paragraph discussing the possible influence of this variant.

Changes in the text: This information was included in the text as suggested (Discussion section, page 10, paragraph 2).

Comment 2:

In addition, it is difficult to clarify whether statin-related myalgia is associated with variants in the SLCO1B1, SLCO1B3, ABCB11, and CYP3A5 genes in this case report.

R: The myalgia reported could be due to the *SLCO1B1* c.521T>C variant, which has been associated in several studies to atorvastatin, simvastatin, and rosuvastatin-related myotoxicity, as shown in a recent review and meta-analysis by Lee et al, 2018, which we referred in the revised manuscript.

As for the remaining variants, there are no reports with conclusive data about their role in statin-related myalgia. However, there are some indications in the literature that point these variants as having a potential role in myalgia. Therefore, we believe that the combination of the patient's deleterious variants affects simultaneous components of the statin pharmacokinetics pathway.

Changes in the text: We included more references and improved the discussion in the revised manuscript (Discussion section, page 9, paragraphs 2 and 3).

Comment 3:

The authors described that Olsson et al. [8] reported that in heterozygous FH patients, LDL-c level reductions of 57% have been observed after a 6-week treatment with rosuvastatin 20 mg. The reviewer thinks that the subjects in this report were patients with not FH but hypercholesterolemia.

R: We appreciate the reviewer´s comment. Indeed, the referred article describes the LDL-c reductions in hypercholesterolemic patients, not FH patients. In place, we referred another study (Stein et al, 2003) that describes an LDL-c reduction of 47.1% in heterozygous FH patients using rosuvastatin 20 mg for 6 weeks.

Changes in the text: We modified the text and reference list (Discussion section, Page 7, Paragraph 1, and Reference 8).

Comment 4:

Did the authors get written informed consent? Please describe about informed consents.

R: As described in the Ethical statement, the patient signed the informed consents to participate in the studies (Page 12, paragraph 1). The DNA sequencing study and the intervention study were approved by the local Ethical Committees and the patient signed the written informed consents for both before her enrollment. In the informed consent of the DNA sequencing study, the patient was informed that her samples would be collected to be used for laboratory and genetic testing. For the intervention study, we informed details about the intervention protocol, including the 6-week wash-out period and statin reintroduction period, and that we would make follow-up calls between each visit. We explained that blood samples would be collected and would be used for laboratory tests, as well as in genetic and epigenetic studies.

Changes in the text: We clarified about the ethical approval and included more information on the informed consents in the Ethical statement (Ethical statement section, Page 12, paragraph 1).

Comment 5:

In introduction section, the authors describes that FH is a monogenic metabolic disease. Recently, it has been reported that 10% of FH is caused by accumulation of SNPs.

R: We thank the reviewer for pointing this out. This information was corrected in the revised manuscript.

Changes in the text: The text was changed as suggested (Introduction section, Page 3, Paragraph 1).

Comment 6:

In Case Presentation, the authors described “While on rosuvastatin therapy, she had a mean LDL-c level of 160 mg/dL.” However, in the first visit (V1), her LDL-C level is 263 mg/dL. Did her pregnancy history cause the elevation of LDL-C level? Please explain.

R: The reported mean LDL-c level is a mean value during 8 years of treatment with rosuvastatin. Rosuvastatin’s dose was increased throughout the years because of the increase in LDL-c levels. We do believe that this is due to the progression of the hypercholesterolemia and it was also affected by her pregnancy history, during which rosuvastatin treatment was interrupted.

Changes in the text: We added this information in the revised manuscript (Case presentation, Page 5, Paragraph 1).

Comment 7:

Was rosuvastatin 20 mg treated during the period between V1 and V2?

R: During the period between V1 and V2, the patient underwent a rosuvastatin wash-out period, therefore she was not treated with rosuvastatin.

Changes in the text: We clarified this information in the revised manuscript (Case presentation section, Page 6, Paragraph 1).

Comment 8:

In Table 1, is nucleotide change of rs776746 6986A>G in CYP3A5 gene?

R: Yes, the nucleotide change is c.6986A>G. We corrected this information in Table 1.

Changes in the text: This information was changed in Table 1 (page 19).

Comment 9:

It will be easier to understand by showing how to analyze pharmacokinetic-related gene variants.

R: We thank the reviewer for the valuable contribution. We have included a figure describing the impact of each variant in rosuvastatin's and other statins' pharmacokinetics, therefore, in statin response and myalgia.

Changes in the text: We included the Figure 2 and added a caption (Section Figure legends, page 17)