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Ezetimibe coadministered with fenofibrate: some safety questions: reply

We thank Dr Borja for interest in our work¹ and this letter allows us to expand on the criteria related to creatine kinase (CK) elevations used in our study. First, it is important to state that there were no measured CK elevations more than 10 times upper limit of normal (ULN), no reports of myopathy, and that the incidence of myalgia was low and similar among all four treatment groups (3.1% for placebo, 1.6% for ezetimibe 10 mg/d, 1.1% for fenofibrate 160 mg/d, and 1.6% for fenofibrate 160 mg/d plus ezetimibe 10 mg/d) over 12 weeks.² Additionally, there were no measured elevations in CK more than five times ULN with or without symptoms with any treatment (one patient in the fenofibrate plus ezetimibe group had one measured CK level between three and five times ULN). The CK criteria used in the current protocol for retesting and discontinuing patients are the same as those used in all lipid lowering protocols over the past several years by Merck & Co., Inc. and Merck–Schering Plough Pharmaceutical. Although the criteria developed by the ACC/AHA/NHLBI² appear reasonable, the CK criteria used in the current protocol have been used extensively during the development of lovastatin, simvastatin, ezetimibe, and ezetimibe/simvastatin.

Conflict of interest: none declared.

References

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I would like to comment on some questions in reference to the article of Dr Farnier and co-workers on the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia.

First, criteria of clinical and/or laboratory muscle-related adverse events are not referenced and are not in accordance with the recently published criteria of the ACC/AHA/NHLBI clinical advisory on the use and safety of statins.² It should be convenient to know why these criteria were used.

Secondly, consecutive elevations of CK > 10 × ULN without muscle symptoms or CK >5 × ULN with muscle symptoms were reasonably defined as adverse events of clinical interest. On one hand, neither time between consecutive determinations of CK nor whether the study drugs should be withdrawn after the first CK elevation are not specified. It should be considered that the levels of the CK decrease ~39% per day after the cause is stopped³ and, thus, depending on the time elapsed between two consecutive determinations, an elevation of CK attributable to the study drugs could be missed. It should be interesting for the reader that what was the time allowed in the study protocol between the first elevation of CK and the second determination. On the other, it should be mentioned that the ACC/AHA/NHLBI clinical advisory on the use and safety of statins² considers that muscle symptoms with increased CK levels are criteria of myositis and advise that in this situation the drug should be discontinued immediately. Of course, it is referred to statins but in the case of fibrates, it does not seem different. For this reason, it is surprising that patients with a first elevation of CK > 5 × ULN with muscle symptoms were allowed to continue being treated with the study medications. This question should be clarified by authors.

Conflict of interest: none declared.

References

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