Letters to the Editor

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Ezetimibe coadministered with fenofibrate: some safety questions

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.1

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 On one hand, neither time between consecutive determinations of CK nor whether the study drugs should be withdrawn after the first CK elevation are not specified.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 statins 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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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.

Word counts imposed by the journal allow us only to summarize the details for all procedures used in this study. Subsequently, we describe in detail the procedures for monitoring and handling elevations in CK used in our study. According to the protocol, the central laboratory will notify an investigational site if CK is more than five times ULN, and the site will then contact the patient for a retest within 3 days of the first blood draw. At the follow-up visit, a patient's history will be evaluated: for potential drug interaction with known inhibitors or substrates of CYP3A4; for any recent unusual and/or strenuous exercise, trauma, or intramuscular injections prior to blood draw; and to rule out myocardial ischaemia. As per the protocol, all patients with elevated CK levels will be followed until resolution. The following criteria for CK elevations were used in this study:

(1) Patients with persistent (two consecutive) CK elevations five-fold or more WITHOUT muscle symptoms were discontinued.
(2) Patients with persistent CK elevations more than 10-fold WITH or WITHOUT muscle symptoms were discontinued.
(3) Patients with a persistent CK elevation five-fold or more and less than 10-fold WITHOUT muscle symptoms may at the discretion of the investigator and with patient monitoring, remain on study drug until a repeat CK is obtained.
(4) Patients with a single CK elevation 10-fold or more WITH muscle symptoms interrupted study drug and had a follow-up CK within 3 days.
(5) Patients with a single CK elevation 10-fold or more WITHOUT muscle symptoms may at the discretion of the investigator and with patient monitoring, remain on study drug until a repeat CK is obtained.

Conflict of Interest: M.F. has no conflict of interest to declare. M.J.D., Y.B.M., and B.G. are employees of Merck & Co., Inc. and may hold stocks or stock options in Merck & Co., Inc.

References

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