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The Author's Reply

We were interested to see this letter from Goldstein and colleagues proposing a possible mechanism by which statins may perpetuate neurodegenerative disorder. As they say, however, a proposed mechanism does not resolve the clinical matter.

It is a great shame that there has been no other correspondence sent for publication in *Drug Safety*, or other major scientific journals, on our work. The purpose of any signal is to raise a question for action by others who are better able to pursue it, to refute it or support it.

We, the authors, have received some views on our signal from around the world, which we summarize here. Much of the correspondence relates to individual letters from or about patients and their problems. The Peoples Pharmacy in the US has a website (www.peoplespharmacy.com) where patients, relatives and health professionals are encouraged to report their experiences on amyotrophic lateral sclerosis (ALS) and statins. There are >200 responses, which are also typical of those we have received, although many do not actually relate to ALS.

The following is a summary of this communicated case data.

- Most of the patients experienced severe myalgia only, which resolved on stopping the statin. However, many of these patients were told by health professionals that the statin had no causative relationship to their problem. Several patients reported that taking enzyme CoQ10 improved their myalgia.
- Some had painless muscles, but severe weakness and wasting. Often, their creatine phosphokinase levels were normal. Patients with this apparent myopathy improved slowly on discontinuing the statin.
- Some patients had a diagnosis of peripheral motor or sensory neuropathy that slowly improved after stopping the statin.
- Some patients had a firm diagnosis of ALS, and mostly did not improve if they stopped the drug. Some of the cases had familial ALS. Only one ALS case, reported by a neurologist, had shown improvement in signs of denervation.
- Several patients started with myalgia and went on to develop a few ALS symptoms. Some described myalgia and/or memory loss, together with difficulty in speaking or swallowing, but no other symptoms of ALS.
- Some patients had diagnoses of myasthenia gravis, but had symptoms which fall into the ALS-like syndrome: difficulty in swallowing, unstable gait and weakness.
- Two patients were diagnosed with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS). This rare MELAS syndrome has some features in common with ALS such as myopathy, paralyses, ataxia and bulbar symptoms (due to strokes). There are also cardiac problems such as cardiomyopathy. The syndrome often affects young people and should be easy to diagnose because of other features. Nevertheless, the two patients who wrote were diagnosed in later adult life, and did not have typical features of the disease.

This information shows that the well known statin-related myalgia and myopathy, even when severe, is not always considered drug-related by physicians treating patients. The patients' reports on neuropathy showing positive dechallenge suggest that peripheral neuropathy may be statin induced, a topic which is still under debate.

The 'ALS cases' seem to have a poor prognosis, and there is nothing more in the correspondence we have received, except the one case with apparent dechallenge, that can argue against a chance relationship. On the other hand, several of the 'ALS patients' seem to have atypical features according to their description, which supports our view that the case definition may be difficult and could lead to clinical problems in diagnosis also.

In the reports above, enzyme CoQ10 was used effectively by several patients with myalgia/myopathy. There is some support in the literature for these observations. For example a paper by Langsjoen et al.[1] records improvement in neuropathy with the use of enzyme CoQ10. In contrast, a recent systematic review did not find the results from such studies

convincing and proposes further trials.[2] A further literature report is interesting since it relates to the possibility that statins may provoke MELAS syndrome.[3] Enzyme CoQ10 has been used as part of the treatment of MELAS. In all, such articles may suggest avenues for further investigation.

None of the above information solves the basic problem of whether there is any causative relationship between statins and central or peripheral neurodegenerative diseases and the incidence of any such association. In our view, the epidemiological challenge is great, and the difficulty may start with the case definition, which leaves open the issue of whether the ALS-like syndrome is a neuropathy or a myopathy, or some combination. Whatever the syndrome is, there is an unresolved matter which is being perpetuated to the public on the web, and in individual case safety reports.

We would be grateful for other opinions to be aired on this topic through open correspondence, whether to argue that the association must be chance, or on the best way forward for a study. If the latter, it might help if a pilot protocol for a formal study could be published in *Drug Safety* for comment and involvement so that this challenge can be dealt with expeditiously, including the best pharmacoepidemiological expertise globally.

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