New Statins Also Produce Fatigue: Spontaneous Reporting as a Complementary System to Increase Safety Knowledge

We have read with interest the Research Letter by Golomb et al1 about the effects of statins on energy and fatigue with exertion. The Research Letter describes the first randomized evidence of these adverse drug reactions (ADRs) for simvastatin and pravastatin, previously reported as anecdotal cases in the literature. The study attracted our attention because it has tied up loose ends after signal detection by pharmacovigilance systems based on spontaneous reporting. Notwithstanding, at the same time it has been a stimulus to look for new data after posing the question “Do the new statins also produce these adverse effects?”

We have reviewed the Spanish Pharmacovigilance System database, which contains more than 193,000 reports of suspected ADRs collected since 1984. The reports involving rosuvastatin (marketed in 2009) had been retrieved and carefully analyzed. Of 263 reports, 9 described asthenia (4 cases), loss of muscular strength (4 cases), or fatigue (1 case) as isolated symptoms (not related with either muscle pain or increase in creatine kinase level). It is to be noted that 6 of 9 patients were younger than 65 years, and 5 of 9 were women taking 5 to 20 mg daily, who had roughly 3 weeks of exposure before the appearance of the ADR. Pitavastatin was marketed in 2011; until March 2012, only 23 reports had been received, and no case of energy or exertional fatigue has been reported.

Musculoskeletal disorders are well-known ADRs of this group of cholesterol-lowering treatments, and severe cases presenting rhabdomyolysis and increase in creatine kinase level have been fully described.2 Mild cases and intolerance to exercise by young athletes have also been described.3,4 Notwithstanding, in our opinion it is important that prescribers keep in mind the possibility that any statin treatment produces these symptoms, especially because they also appear in young patients (ie, those prone to practice any sport).

Whenever possible, the pharmacological treatment of hyperlipidemia should be accompanied by a nonpharmacological approach (eg, to avoid a sedentary life and to exercise). If unnoticed, these ADRs of statins could prevent the benefits of exercise because of fatigue and pain, so knowledge of these adverse reactions of new drugs improves treatment objectives. However, health professionals continue to play an essential role in completing the safety profile of any new drug through ADR reports.

In reply

We concur with Tarapués and colleagues. An analysis we conducted of patient reports of muscle problems (including fatigue)1 is in agreement with their Spanish data, extending fatigue adverse effects (AEs) to all statins. These data suggest that risk approximately parallels statin potency, as does our recent analysis of the US Food and Drug Administration AE reports focused on muscle-related AEs,5 although this latter analysis did not expressly address fatigue.

We agree that AE reporting by physicians is important. We add that patient reporting is important as well. Physicians sometimes dismiss a drug relationship for AEs unfamiliar to them.3 Heeding patient reports has been shown to lead to the same AEs being identified, but often sooner.4 Patient reports and attributions of AEs have been found to be generally reliable, and the European Union has recently adopted patient reporting for all its pharmacovigilance databases (http://ec.europa.eu/health/human-use/pharmacovigilance/developments/index_en.htm). Because statins can have bidirectional effects on many outcomes (eg, causing or protecting against proteinuria) that are associated with variable predominance of prooxidant vs antioxidant effects,5,6 randomized controlled trials (RCTs) can miss causal AE occurrence. Moreover, RCT participant selection practices may lead persons most at risk of AEs to be excluded. Adverse events that may be focused in cer-
taint participant groups (owing to “effect modification”) are important to recognize, even when the average observed effect of a drug has not been noted to be deleterious—in the RCT samples thus far examined. The impact to the person experiencing a problem is real whether or not the effect is “typical,” and recognition of the possible connection to the drug is essential to enable actions to be taken (like drug discontinuation) that may reduce ultimate disability. In short, we concur that AE reports can presumptively identify AEs before they are identified in an RCT setting and add that including patient reports may hasten this.

Finally, Tarapües et al observe that “these ADRs of statins could prevent the benefits of exercise” and urge that exercise accompany statin use. A caveat to this excellent point is that, in the setting of mitochondrial compromise, which statins can foster, exercise may worsen the energy supply-demand imbalance, potentiating risk (or severity) of statin muscle injury. This is another reason to focus statin use (indeed, preventive drug use generally) in those for whom evidence shows definite expectation of net benefit to the patient, judged by outcomes, such as all-cause mortality, that objectively balance risk and benefit.

Beatrice A. Golomb, MD, PhD
Sabrina Koperski, BS

Author Affiliations: Departments of Medicine (Dr Golomb and Ms Koperski) and Family and Preventive Medicine (Dr Golomb), University of California, San Diego, La Jolla. Correspondence: Dr Golomb, Department of Medicine, University of California, San Diego, 9500 Gilman Dr, Mail Code 0995, La Jolla, CA 92039 (bgolomb@ucsd.edu).

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Jehovah’s Witnesses May Not Have Identical Outcomes With Nontransfused Non-Witnesses After Cardiac Surgery

In an attempt to investigate the effect of current extreme blood management strategies on outcome of patients undergoing cardiac surgery, Pattakos et al1 used, what they called, the “natural experiment” of Jehovah’s Witnesses, who refuse blood transfusions owing to religious beliefs. They performed a statistically elaborate analysis of operative and long-term outcomes in Witnesses compared with propensity-matched patients who received transfusions. They concluded that extreme blood management strategies do not appear to place patients at heightened risk for operative mortality and morbidity nor reduce their long-term survival. As a matter of fact, their analysis demonstrated that Witnesses had a relatively improved overall outcome, ie, a lower operative morbidity and, in long-term follow-up, a lower risk of death in the early hazard phase. Hence, this report corroborates other observational studies indicating that transfusions are associated with negative outcomes following cardiac operations.2,3

Nonrandomized studies suffer from the uncertainty of potential unmeasured patient or procedure-related variables influencing the results.4 Besides unknown confounders, however, an inherent lurking variable should be considered in this study: religious belief per se. There is some evidence suggesting a conscious or subconscious modification of operative technique to ensure better hemostasis in Jehovah’s Witnesses. Despite “postoperative liberal use of additional operation for bleeding”5(p1354) that the authors state as one of blood conservation practices, Witnesses were not taken back to the operating room more frequently than non-Witnesses. Contrariwise, non-Witnesses were nearly twice as likely to undergo additional operation for bleeding or tamponade (7.1% vs 3.7% in matched groups; Probability of 0.03).1 Intriguingly, perioperative myocardial infarction was also significantly more frequent in non-Witnesses (2.8% vs 0.3% in matched groups; Probability of 0.01). More meticulously performed anastomoses with the intent to be more hemostatic may plausibly account for this difference. Obviously, extra meticulous operative technique can be a key factor affecting operative and long-term outcome.

It would be interesting to know whether the results attained in Jehovah’s Witnesses are identical to matched non-Witnesses who were not transfused. Lack of pertinent data casts doubt on the external validity and, hence, the final conclusion of the study. Operative and long-term outcomes of patients who are not eventually transfused do not necessarily match outcomes of patients for whom transfusions are not permitted.

Dimitrios C. Angouras, MD

Author Affiliation: Department of Cardiac Surgery, Athens University School of Medicine, Attikon University Hospital, Athens, Greece. Correspondence: Dr Angouras, Department of Cardiac Surgery, Athens University School of Medicine, Attikon University Hospital, 1 Rimini St, Chaidari, Athens 12462, Greece (dangouras@yahoo.com).

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3. Surgener SD, Kramer BS, Olmscheid EM, et al; Northern New England Cor-

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