Author’s Reply

Statin Intolerance and Vitamin D Supplementation

Recent epidemiologic studies have added substantial support to the hypothesis that vitamin D deficiency modifies the risk of musculoskeletal symptoms experienced with statin use.\(^1\)\(^-\)\(^3\)

We recently reported studies in 74 men and 72 women intolerant to ≥2 statins because of myalgia, myositis, myopathy, or myonecrosis, found to be vitamin D deficient. Their statin intolerance was safely resolved in most cases (88-95%) by vitamin D supplementation (50,000-100,000 units/week).\(^4\) Backes et al.\(^4\) have reported that in 34 patients intolerant to three or more statins, repletion of serum vitamin D to ≥30 ng/ml (median 44 ng/ml) allowed 18 (53%) patients to “…utilize some form of alternative or daily statin dosing or a higher dose for at least 4 months…” Plausible reasons for the difference in resolution of statin intolerance in these two reports\(^4\),\(^5\) included a higher serum vitamin D on treatment in our\(^4\) versus their\(^5\) study (53-55 vs. 44 ng/ml), and our predominant use of Crestor, a well-tolerated statin,\(^6\) as the challenge statin after vitamin D repletion.

Although we have not done a formal dose-response study with vitamin D supplementation in recent report of 146 statin-intolerant patients with low serum vitamin D (<32 ng/ml) at study entry,\(^4\) the higher the serum vitamin D within the normal range on vitamin D supplementation, the greater the likelihood of being able to tolerate the re-challenge statin without myalgia-myositis. On vitamin D (50,000-100,000 units/week for a median duration of 14 months), 131 of the 146 patients (88%) were free of myalgia, on the re-challenge statin, but 15 (12%) still had myalgia and could not tolerate the re-challenge statin. Comparing these two groups, there were no differences (\(P > .05\)) in age, race, gender and vitamin D at pre-treatment study entry, but the myalgia-free group had higher serum vitamin D after 14 months of vitamin D supplementation (55 ± 20, median 53, vs. 42 ± 13, median 36 ng/ml, \(P = .005\)). Serum vitamin D also increased more in the myalgia-free than myalgia persistent group (33 ± 21, median 30, vs. 21 ± 13, median 18 ng/ml, \(P = .02\)). With myalgia (no vs. yes) after 14 months of vitamin D supplementation, by stepwise logistic regression, with explanatory variables such as race, sex, age and serum vitamin D at study entry, serum vitamin D at follow up, and change of serum vitamin D on treatment from baseline were significant independent predictors of statin tolerance without myalgia, \(P = .02\). For each unit higher in serum vitamin D, statin tolerance increased (OR = 1.04, 95% CI, 1.007-1.078; AUC = 0.726).

Given the high likelihood of substantial placebo effect\(^4\),\(^7\),\(^9\) of vitamin D supplementation in vitamin D deficient, statin-intolerant patients, we have repetitively and consistently\(^4\),\(^7\),\(^9\) emphasized the importance of definitive placebo-controlled, double blind studies. Within this frame of reference, The ODYSSEY ALTERNATIVE, a randomized phase 3 trial\(^10\) is of seminal importance. Total 314 statin intolerant subjects (unable to take ≥2 statins because of muscle-related adverse events [AES]) first received single-blind subcutaneous and oral placebo for 4 weeks, and were removed from the subsequent study if they developed muscle-related AES on placebo.\(^10\) Continuing patients were randomized (2:2:1 ratio) to Alirocumab 75 mg every two weeks, or Ezetimibe 10 mg/day, or Atorvastatin 20 mg/day for 24 weeks.\(^10\) The Alirocumab dose was increased to 150 mg every 2 weeks at week 12 depending on week 8 LDL-C levels.\(^10\) In data presented as an American Heart Abstract in 2014,\(^11\) 6.9% of subjects were excluded in the placebo run-in, establishing a threshold (without statins) of muscle AES. As noted by Backes et al.,\(^5\) “…75% of the previously intolerant patients tolerated the Atorvastatin 20 mg daily for the duration of the 24-week study period.”\(^5\) Backes et al.\(^5\) concluded that “…such results strongly highlight the subjectivity of statin intolerance and the major influence of a placebo effect in many patients.” Of great importance, the preliminary data\(^11\) presented for the ODYSSEY ALTERNATIVE study, suggests that Alirocumab\(^10\) will be effective and well tolerated in patients who were statin-intolerant due to muscle AES.

Vitamin D supplementation appears to benefit a majority of statin intolerant, vitamin D deficient patients, and some of the benefit arises from placebo effect. However, statin-induced myalgia has been reported...
in 27% of subjects treated with statins,[12] and vitamin D supplementation allows a majority of previously statin-intolerant patients to take enough statins consistently enough to reach current LDL targets.[4] When the PCSK9 drugs become available, as suggested by preliminary evidence[11] from ODYSSEY ALTERNATIVE (Alirocumab),[10] we speculate that they will provide a paradigm shift in the treatment of statin intolerance.

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Conflicts of interest
There are no conflicts of interest.

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