

# Statin Intolerance and Vitamin D Supplementation: Sunny, but a Few Clouds Remain...

Dear Editor,

We read with interest the article by Khayznikov *et al.*, regarding the resolution of statin intolerance with vitamin D repletion.<sup>[1]</sup> We too have tried this strategy among a similarly statin intolerant population (median – three previous statins) and believe vitamin D supplementation plays a role in treating certain individuals. Our results demonstrated that vitamin D repletion to >30 ng/ml, allowed 53% (18/34) of the intolerant patients to utilize some form of alternative or daily statin dosing or a higher dose among those receiving a statin but experiencing tolerable symptoms, for at least four months (mean follow up 8.5 + 4.4 months). Our findings are encouraging but well below the 88-95% statin tolerability rates reported in the present study.

Directly comparing study populations and results is not feasible; however, one potential explanation for response differences may be the vitamin D level achieved. For instance, the vitamin D levels among those tolerating the statin rechallenge in our group was 44 ng/ml compared to 53-55 ng/ml in the current report, suggesting that perhaps our vitamin D repletion was incomplete, despite each group falling within the range suggested by the Endocrine Society.<sup>[2]</sup>

Another factor that we believe played a prominent role in the resolution of myalgic symptoms in the current study was the predominant utilization of rosuvastatin. The authors recognize that rosuvastatin is less frequently associated with myotoxicity; however, this should not be minimized. In fact, the same research center performed a similar study, and determined that the vast majority of previously statin intolerant subjects reported no adverse effects when rechallenged with rosuvastatin 5-10 mg daily.<sup>[3]</sup>

Lastly, we agree with the authors that an optimal study evaluating statin intolerance would be blinded and placebo-controlled, given the subjective nature of most myotoxicity. In fact, this design was recently utilized to assess various lipid-altering agents, including the

investigational proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, among subjects unable to tolerate two or more different statins because of unexplained muscle-related symptoms.<sup>[4]</sup> After successful completion of a four-week single-blind placebo run-in period, subjects were randomized in a double-blind manner to a PCSK9 injection Q two weeks + oral placebo daily, ezetimibe 10 mg daily + placebo injection Q two weeks, or atorvastatin 20 mg daily + placebo injection Q two weeks, for 24 weeks. Such a study design provided novel, insightful, and revealing findings with regard to statin intolerance. For example, the trial demonstrated that 6.9% of subjects were excluded from randomization due to muscle-related adverse events during the placebo run-in period. Further, 75% of the previously intolerant patients tolerated the atorvastatin 20 mg daily for the duration of the 24-week study period. Such results strongly highlight the subjectivity of statin intolerance and the major influence of a placebo effect in many patients.

Statin intolerance, especially among patients with previous sensitivity to multiple agents, is a complex and poorly understood issue that remains a clinical challenge. In the present study, vitamin D repletion likely improved muscle function and resolved symptoms in some patients. However, the vitamin D supplementation may have also provided a placebo effect, while the utilization of rosuvastatin further enhanced response.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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