Statin-associated muscle symptoms: beware of the nocebo effect

Patient-reported statin intolerance, predominantly due to statin-associated muscle symptoms (SAMS), is a common and difficult-to-manage condition affecting millions of patients worldwide.[1] Different expert panels have proposed various definitions and classifications for statin intolerance.[2,3] However, the development of SAMS does not necessarily signify statin intolerance since statin therapy might not always be pharmacologically involved. Moreover, some patients with SAMS might be able to tolerate a lower dose than the dose that leads to SAMS, longer dose intervals, or an alternative statin.[4] Furthermore, the clinical spectrum of SAMS includes a heterogeneous group of clinical signs, symptoms, and laboratory findings, ranging from an asymptomatic rise in serum creatine kinase concentration or myalgia to more severe painful myositis and, rarely, fatal rhabdomyolysis.[1] When muscle symptoms are accompanied by a biochemical substrate, such as in rhabdomyolysis, or a histological substrate, such as in necrotising myopathy, their diagnosis and relationship with statin therapy can be obvious. However, problems arise when patients present only mild myalgia, one of the most frequent SAMS. This clinical scenario requires expertise because the nocebo effect needs to be considered in this context5. Thus, an understanding of SAMS is imperative given the large and growing number of patients eligible for statin therapy, as stated in the European and American guidelines for cardiovascular prevention.

Ajay Gupta and colleagues[6] report a highly relevant study in *The Lancet* in support of the fact that statins do not significantly increase the risk of muscle pain. They compared adverse event (AE) rates during a blinded randomised atorvastatin therapy phase when atorvastatin 10 mg daily was compared with placebo with those during a non-blinded non-randomised statin therapy phase when patients were offered open-label statin using an identical follow-up procedure and AE ascertainment process in the same population in the Lipid-Lowering Arm (LLA) of the Anglo-Scandinavian Cardiac Outcomes Trial. The main finding was that no excess of muscle-related AEs was reported among patients receiving atorvastatin therapy during the blinded randomised period (298 [2·03% per annum] in the atorvastatin group *vs* 283 [2·00% per annum] in the placebo group; hazard ratio 1·03 [95% CI 0·88–1[21·; p=0·72). However, a significant excess in muscle-related AEs was reported when patients (and physicians) knew that they were taking a statin during the non-blinded phase (161 [1·26% per annum] *vs* 124 [1·00% per annum]; 1·41 [1·10–1[79·; p=0·006).

Muscle-related AE rates are often argued to be low in randomised controlled trials owing to patient selection. Thus, the strengths of Gupta and colleagues' study lie in the fact that these were the same patients, no run-in period existed to exclude patients intolerant to therapy, and few patients had

previously taken any statins. Additionally, the atorvastatin dose typically used in the non-blinded phase was the same as in the blinded phase.

The excess of muscle-related AEs associated with atorvastatin therapy only when the comparison was non-blinded is consistent, at least in part, with a nocebo effect.[6] In other words, when drug therapy was blinded, the nocebo effect applied equally to the statin and placebo groups of the trial. The term nocebo was coined by Walter Kennedy in 1961 to denote the counterpart to the use of placebo.[7] The nocebo effect reflects changes in human psychobiology involving the brain, body, and behaviour rather than drug toxicity. Reports of SAMS might result from patients' perceptions about statins in light of negative press reports of statin use[8,9] or even poor understanding of warnings about statin-associated side-effects.[10] SAMS can lead to poor treatment adherence or even statin discontinuation, which is associated with increased cardiovascular risk leading to higher rates of heart attacks, strokes, and cardiovascular mortality.[8,9] Therefore, clinicians should be fully informed about potential nocebo effects, including patients' previous knowledge or perceptions of statin therapy, and discuss the evidence for SAMS with patients.

The Anglo-Scandinavian Cardiac Outcomes Trial population, from which Gupta and colleagues' conducted their study, came from the UK, Ireland, and Scandinavia, and was predominantly older than 60 years of age, male, and of European descent; additionally, the statin was low-dose atorvastatin. Therefore, the results cannot be extrapolated to older populations, different ethnicities, other statins, or higher doses.

Fewer patients could possibly report SAMS with statins if they receive the medication blindly than if they receive it open label, or they might have SAMS even if they received a placebo, indicating a highly improbable pharmacological basis. Since the nocebo effect occurs frequently and is under-recognised in clinical practice, physicians should be informed of how to recognise and manage this effect.[11] Evidence from the Understanding Statin Use in America and Gaps in Education survey, seeking predictors of statin adherence, switching, and discontinuation, underlines the importance of a trustful physician-patient relationship, since only a few patients will believe that their SAMS are of psychogenic origin.[12] Given that statins are among the best evidence-based lipid-lowering tools available and suitable for many patients, prevention of intolerance is paramount. Thus, physicians should alert their patients to possible statin-associated side-effects without raising negative expectations. Furthermore, they should encourage patient understanding of the rationale for statin treatment, which could optimise and facilitate shared decision making on statin therapy.

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