Statins and myalgia: fact or fiction?

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Contemporary guidelines have lowered the threshold for statin use in primary prevention (7.5% risk of a cardiovascular event over 10 years in the USA,[1] 10% risk according to National Institute for Health and Care Excellence [NICE] guidelines in the UK).[2] Applying these thresholds, the majority of men over 50 years and more than half of women over 60 years will qualify for statin use. Countering the more widespread uptake of statin use in primary prevention advocated by these guidelines are claims, popularised by the lay press and uncritically published in some medical journals,[3,4] that statin use is accompanied by an unacceptable incidence of side effects that adversely compromise lifestyle and which challenge whether the small absolute benefits in some lower risk groups are worth the intolerance of the statin.

So what are the facts? Before discussing the data, it is important to distinguish between severe muscle-related events (myopathy and rhabdomyolysis) and less severe muscle aches and pains (myalgia) – the former being associated with marked elevation in creatine kinase levels, in contrast with the latter, which is not. All statins can cause myopathy, but the incidence is low – about 0.1%. This compares with an incidence of about 0.04% on placebo. Rhabdomyolysis is much rarer.[5] Preclinical studies show that statins decrease mitochondrial function, attenuate energy production and alter muscle protein degradation, thereby providing a mechanistic explanation for a potential link between statin use and muscle symptoms. Moreover, an increased frequency of rare pathogenic variants in muscle disease-associated genes has been reported to be associated with a substantial increase (up to 20-fold) in subjects with severe myopathy.[6,7] Pharmacokinetic interactions of statins with inhibitors of cytochrome P450 isoenzymes will also increase the risk of myopathy.

There is, however, no evidence that these molecular mechanisms are responsible for the more generalised aches and pains, without evidence of creatine kinase elevation, reported in clinical practice.

The debate

The critical debate arises from the discrepancy between the outcomes reported from randomised, double-blind, placebo-controlled trials and

observational data on less severe muscle symptoms (myalgia) in everyday clinical practice.

Let us first consider the trials. Most trials report severe adverse drug reactions and withdrawals from drug treatment where, with the exceptions noted above for myopathy, there is no difference in safety outcomes for statin treatment and placebo. Few trials have, however, adjudicated non-serious adverse events (AEs). Two trials have systematically reported muscle symptoms. In the Heart Protection Study,[8] muscle symptoms were recorded after direct questioning at each visit. In both the simvastatin group and the placebo group, 6% of patients reported muscle aches or pains at each visit and 33% of patients in each treatment group reported similar symptoms at least once during the study. In JUPITER,[9] the incidence was somewhat lower, but similar in both statin- and placebo-treated arms of the trial.

Certain criticisms of the trials have been raised. First, few trials have reported and adjudicated AEs. This is not required by regulatory bodies. The number of such events – more than 300,000 in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) – is large and few trialists have subjected them to systematic evaluation. Second, in some trials, apparently statin-intolerant patients were excluded following a pilot run-in on statin. Third, that trial sponsors could have influenced the reporting of the results of trials and downplayed the side effect profiles of the drugs.

Observational studies contrast dramatically with the outcomes of controlled trials. Of patients taking a statin, 10–20% or more have been reported to complain of muscle-related side effects – pain or weakness (myalgia).[6] The causal association of these symptoms with statin use has not, however,

been established. Regrettably, certain authors,[3,4] have deliberately misrepresented the claims of Zhang and colleagues[10] that statins were causally related to side effects in 20% of cases. Zhang *et al.* reported on discontinuation of statins in routine clinical practice in a large cohort of over 100,000 patients. Statin-*related* events were documented in 17.4% of patients, but more than 90% of those who were re-challenged with a statin were taking a statin 12 months after the related event. Zhang and colleagues concluded that many of the statin-related events had other causes, and this is consistent with the view that non-pharmacological mechanisms are responsible for the intolerance.

In a separate study, reported recently,[11] re-challenge of patients previously withdrawn from a statin because of myalgia, was associated with the return of identical symptoms in both statin- and placebo-treated patients. A further study,[12] recruited over 300 patients intolerant of at least two statins due to muscle symptoms. They were randomly allocated, double-blind, to either a proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody, alirocumab, or ezetimibe or atorvastatin. Equal numbers (about 20%) from each group withdrew due to muscle-related side effects, and about 80% in each group reported no side effects of any kind leading to discontinuation during follow-up. The evidence for a causal link between statin use and myalgia is, thus, extremely difficult to establish in the vast majority of patients.

Damage done

The *BMJ*, which published the unsubstantiated claims of Abrahamson *et al*.[3] and Malhotra,[4] that the association was causal, was persuaded by an independent review body to retract these implications. Nevertheless, the damage had already been done and, along with extensive media reports on the side effects of statins, public confidence in the drugs was compromised with the result that patients discontinued their statins, or were unwilling for them to be prescribed. Regrettably, this has impacted on those recommended statins, not only for primary prevention, but also for those who had already experienced a cardiovascular event in whom, of course, the risk of a future event is much higher and the absolute risk reduction with statins is much greater.

There are few areas of medicine where there seems to be such a discrepancy between the results of controlled trials and the observations from clinical practice and, while there are many differences between the populations under investigation and the manner in which the information is recorded, one of the key differences is whether or not patients knew they were taking a statin.

In order to shed further light on this extraordinary controversy we intend to take advantage of the unusual experience of the ASCOT study in which patients were initially randomised to one of two blood-pressure-lowering strategies (ASCOT-BPLA),[13] and then by way of factorial design re-randomised to a statin, atorvastatin or placebo (ASCOT-LLA).[14] ASCOT-LLA was a double-blind trial that was stopped prematurely after 3.3 years of follow-up due to a highly significant risk reduction in the primary end point of non-fatal myocardial infarction and fatal cardiovascular disease. Patients were then offered open-label atorvastatin and continued in the blood pressure arm of the trial for a further 2.2 years when the trial was terminated. Approximately two thirds of patients who were formerly assigned atorvastatin or placebo took the statin for the remainder of the trial.

In addition, to the recording of serious AEs and withdrawals from treatment, non-serious AEs were documented at each visit throughout the trial. A database of more than 300,000 AEs has been cleaned by observers ignorant of medication assignment, and will be interrogated for evidence of muscle-related symptoms and other AEs putatively associated with statin treatment. The patient population and the methodology applied to establish whether or not there is an association between statin use and the development of a particular AE will be derived for those on blinded and unblinded treatment in an identical way. The results of our analyses, which should be available later this year, will hopefully shed further light on the current ongoing controversy.

In the meantime, the high incidence of statin-related symptoms demands a practical and pragmatic approach to their management. The European Atherosclerosis Society proposes the following:[7] withdraw statin followed by one or more re-challenges after a washout. (This helps to establish causality.) Try alternative statin, a statin at lowest dose, intermittent dosing of highly effective statin (alternate days or twice weekly), or the use of non-statin lipid-lowering drugs.

Other risks

It was beyond the brief of this commentary to consider other putative AEs associated with statin treatment. For most, if not all, reports from observational studies are at variance with those obtained from double-blind, controlled clinical trials, in which there is no evidence, for example, of excess of erectile dysfunction, worsening memory or dementia with statins. These observations will be further explored in ASCOT. The exception is the development of new-onset diabetes, for which there was a 9% excess compared with placebo in a meta-analysis of randomised trials.[15] This was related to dose and potency of the statin and was confined to those who had at least one risk factor for diabetes. One new case per 1,000 years of statin treatment. Over a four-year period statins prevent nine new vascular events for each case of new-onset diabetes. Powerful evidence that the risk:benefit ratio is strongly in favour of statin use.

The debate and controversy will no doubt continue. The reporting of bad science and its popularisation by the lay press is a hindrance to optimal practice. The MMR (measles, mumps and rubella) vaccine scandal is a typical example. As clinicians, we have a responsibility to educate our patients, and, hopefully, new findings will add to the weight of evidence in support of the efficacy, safety and tolerability of statins

Conflict of interest

The author was co-chairman of ASCOT and received grant support for the conduct of the trial and speaker engagements from Pfizer.

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