Assessing Muscle-Related Adverse Events in Randomized Trials of Statins

INTRODUCTION

There is debate over the frequency and causal relationship between statins and muscle-related adverse events (MRAEs). Postmarketing observational studies have suggested such symptoms are very common, affecting around 20% of patients. However, meta-analyses of randomized trials have recorded a far lower incidence of MRAEs (around 5%), with no suggestion of a clear causal relationship. Some have posited that the discrepancy in rates of adverse events may in part be due to inadequate data collection in trials. This could occur if passive approaches (relying on spontaneous reports from patients) to MRAE data collection were used, as is common in trials, instead of proactive approaches (e.g., standardized checklists).

METHODS

We requested internal company trial documents from regulators—clinical study reports (CSRs), trial protocols, and blank case report forms—to determine if and how MRAEs were prospectively assessed in randomized trials of statins. We obtained these trial documents through freedom of information requests to the European Medicines Agency and Health Canada for all clinical trials of atorvastatin, rosuvastatin, fluvastatin, and simvastatin. We included all blinded, placebo-controlled randomized trials irrespective of year. For all included studies, we assessed each study’s inclusion and exclusion criteria to determine whether participants may have been precluded from participating in a trial because of treatment-related adverse events, either historically or through pre-randomization run-in procedures.

We examined study protocols and blank case report forms to determine whether study investigators were instructed to survey MRAEs and their severity. We also recorded whether rhabdomyolysis, myalgia, and other MRAEs were specifically reported in trial results. Any investigation of creatine phosphokinase (CPK) levels was noted. Data extraction was performed in duplicate, with discrepancies resolved through discussion. Our dataset is publicly available (https://doi.org/10.5281/zenodo.5196179).

RESULTS

We obtained and screened documents for 85 trials; 23 trials of 4 statins met our inclusion criteria. The median number of randomized participants of the 23 trials was 175, and the median female percentage was 38%. Two trials excluded individuals with a history of MRAEs. A further 19 trials allowed clinician judgment about the appropriateness of patient eligibility (e.g., “Patients with other significant abnormalities that the investigator feels may compromise the patient’s safety or successful participation in the study must not be entered into the study.”). Twelve trials had a placebo run-in period; five trials had an active run-in period. All trials recorded the intensity and duration of adverse events (Table 1). However, only one trial had a dedicated MRAE surveillance and reporting system, and 17 trials examined CPK levels linked to MRAE reporting.

Seventeen trials reported at least one type of MRAE (Table 1). Most MRAEs were generally not defined. Unspecified joint pain/disorder, leg pain/disorder, and miscellaneous pain were the most commonly reported MRAEs from the included statin trials, besides rhabdomyolysis and myalgia.

DISCUSSION

While the majority of trials 89% (17/19) reported at least one type of MRAE, only one trial had proactive methods for soliciting these data, suggesting the vast majority of trials used passive methods for MRAE data collection. Passive methods are known to underrate adverse events, and may help explain the lower reporting of MRAEs in trials compared to clinical experience. In addition, the use of active drug run-ins in trials (particularly for atorvastatin) would further diminish the ability of those trials to detect the frequency of MRAEs.

Our results underscore the importance of critical appraisal of trial design and data collection methods from CSRs, and simultaneously the vulnerability of any meta-analysis that skips this step.

Amongst all clinical trial data held by regulators for four major statins, only one trial proactively collected data
Table 1 MRAE Data Collection and Reporting Across Trials

| Trial reporting | Atorvastatin | Rosuvastatin | Fluvastatin | Simvastatin |
|----------------|-------------|--------------|-------------|-------------|
| Methods for recording AEs (any type) | | | | |
| Intensity of AEs assessed | 6 (100%) | 2 (100%) | 11 (100%) | 4 (100%) |
| Duration of AEs assessed | 6 (100%) | 2 (100%) | 11 (100%) | 4 (100%) |
| Methods for recording MRAEs | | | | |
| CPK lab assessment | 6 (100%) | 2 (100%) | 5 (45%) | 4 (100%) |
| MRAE symptom specific data collection | 0 (0%) | 1 (50%) | 0 (0%) | 0 (0%) |
| Trial results available | 6 | 1 | 9 | 3 |

*The following studies were excluded from the ‘Trial reporting’ section of this table due to incomplete data, redacted information related to AEs, or lack of access to trial results: JUPITER, Study No. 6, Study No. 12, and 4S trial

*A trial was only counted in the tally if it reported at least 1 event of a given type. Trials reporting zero events as well as trials that did not report on the given type were not counted in the tally.

regarding MRAEs, indicating that regulators lacked high-quality evidence necessary to make an informed assessment about the true incidence of MRAEs. Given the clinical importance of the question, regulators should warn about this gap in the knowledge base and encourage future trials to address this data gap.

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Data Availability: Data extractions are freely available in the Zenodo repository (https://doi.org/10.5281/zenodo.5196179).

Declarations:

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