# Investigation of pitavastatin-associated muscular and renal adverse events compared to other statins: Cases from the Food and Drug Administration adverse event reporting system database

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## BACKGROUND

- Muscular and renal adverse events associated with statins using the Food and Drug Administration adverse event reporting system (FAERS) database have previously been reported by Sakaeda et al. [1]. However, Sakaeda et al. [1] investigated the said adverse events associated with all statins except for pitavastatin.
- To our knowledge, no previous study has investigated potential muscular and renal adverse events associated with statins including pitavastatin in the US using FAERS.

## OBJECTIVE

- ***To identify muscular and renal adverse event reports associated with the use of pitavastatin compared to other statins using the Food and Drug Administration adverse event reporting system (FAERS) database.***

## METHODS

***Adverse event dataset***

- FAERS is a spontaneous reporting database.
- Initial and follow-up reports with identical primary linked identification number were taken as a unique patient case report. In the event multiple reports with a common case number were identified, only the safety report with the most recent date was used.
- Reports occurring in foreign countries were excluded not only to focus on US reports but also to remove variation caused by FDA requirements for foreign reporting and different national systems for post-marketing surveillance data.

***Adverse event and drug terms***

- Individual case reports were identified when their reported adverse events were comparable to the selected medical dictionary for regulatory activities (MedDRA) preferred terms (PTs) available from FAERS database. Myalgia, myopathy, rhabdomyolysis and increase in creatine phosphokinase level were identified as muscular adverse events. Acute renal failure, non-acute renal failure and increase in blood creatinine level were identified as renal adverse events.
- Reports listing pitavastatin, simvastatin, atorvastatin, rosuvastatin, lovastatin, fluvastatin and pravastatin as the suspect drug were extracted from FAERS.

***Bayesian Confidence Propagation Neural Network Methodology (BCPNN)***

- BCPNN examines the association between the drug and adverse event using a measure of disproportionality called the Information Component (IC) [2].
- A potential signal for the drug-associated adverse event is identified when the lower limit of the 95% two-sided confidence interval of the IC, denoted by $IC_{025}$ exceeds zero [2].
- Positive IC values indicate that there is a greater likelihood that the combination of drug-associated adverse events was reported more often in the database than statistically expected in the database [2]. Whereas, negative IC values indicates that the drug-associated adverse event combination cases are reported less than statistically expected in the database [2].
- A retrospective data mining analysis was applied to the FAERS database for reports listing the drug names and adverse events were extracted from pitavastatin's FDA approval date (November 23, 2009) through the first quarter of 2012, since at the time when this study was conducted data after the first quarter of 2012 were not available.

## RESULTS

- A total of 957,459 unduplicated US reports were identified since the pitavastatin's approval date through the first quarter of 2012.
- A total of 75,203, 14,242, and 19,149 reports concerning statins, muscular, and renal adverse events, respectively, were extracted during the study time period from FAERS.

**Tables 1 and 2. Signal detection for statin-associated muscular and renal adverse events in the US from the FDA adverse event reporting system database.**

| | | Statin-associated myalgia | | Statin-associated myopathy | | Statin-associated rhabdomyolysis | | Statin-associated increase in creatine phosphokinase | |
|---|---|---|---|---|---|---|---|---|---|
| Statins | Number of statin drug reports | Combination reports | IC ($IC_{025}$) | Combination reports | IC ($IC_{025}$) | Combination reports | IC ($IC_{025}$) | Combination reports | IC ($IC_{025}$) |
| Pitavastatin | 150 | 15 | 2.79 (2.00) | 1 | 1.41 (-2.33) | 5 | 2.88 (1.40) | 10 | 3.95 (2.94) |
| Lovastatin | 3398 | 95 | 1.26 (0.95) | 6 | 1.70 (0.37) | 25 | 2.06 (1.43) | 11 | 1.34 (0.38) |
| Fluvastatin | 313 | 18 | 2.16 (1.44) | 0 | -0.35 (-11.01) | 4 | 2.14 (0.46) | 3 | 2.01 (0.02) |
| Pravastatin | 5398 | 205 | 1.70 (1.49) | 7 | 1.38 (0.16) | 27 | 1.54 (0.94) | 15 | 1.17 (0.35) |
| Simvastatin | 22342 | 721 | 1.48 (1.36) | 58 | 2.50 (2.12) | 460 | 3.62 (3.49) | 124 | 2.20 (1.94) |
| Atorvastatin | 25300 | 2040 | 2.80 (2.73) | 73 | 2.66 (2.33) | 143 | 1.76 (1.51) | 229 | 2.91 (2.72) |
| Rosuvastatin | 18302 | 1180 | 2.47 (2.39) | 35 | 2.05 (1.55) | 236 | 2.94 (2.75) | 157 | 2.82 (2.59) |

| | | Statin-associated acute renal failure | | Statin-associated increase in blood creatinine level | | Statin-associated non-acute renal failure | |
|---|---|---|---|---|---|---|---|
| Statins | Number of statin drug reports | Combination reports | IC ($IC_{025}$) | Combination reports | IC ($IC_{025}$) | Combination reports | IC ($IC_{025}$) |
| Pitavastatin | 150 | 1 | 0.09 (-3.64) | 0 | -0.91 (-11.56) | 1 | -0.52 (-4.25) |
| Lovastatin | 3398 | 81 | 1.95 (1.61) | 19 | 0.91 (0.19) | 140 | 1.89 (1.63) |
| Fluvastatin | 313 | 12 | 2.38 (1.47) | 3 | 1.31 (-0.67) | 29 | 2.90 (2.34) |
| Pravastatin | 5398 | 120 | 1.86 (1.58) | 37 | 1.21 (0.70) | 208 | 1.80 (1.59) |
| Simvastatin | 22342 | 577 | 2.09 (1.96) | 222 | 1.76 (1.56) | 985 | 2.00 (1.90) |
| Atorvastatin | 25300 | 366 | 1.25 (1.10) | 157 | 1.09 (0.85) | 868 | 1.64 (1.53) |
| Rosuvastatin | 18302 | 165 | 0.57 (0.33) | 96 | 0.84 (0.53) | 284 | 0.49 (0.31) |

## DISCUSSION

- Muscular and renal adverse events associated with statins have previously been reported [1,3].
- The application of BCPNN in this study was used solely for hypothesis generation and identification of potential signals and not to draw final conclusions regarding statin-associated muscular and renal adverse events.
- Consistent with the International Society of Pharmacovigilance and International Society for Pharmacoepidemiology guidelines [4], our study reports available information from FAERS.
- Until further evidence establishing a causal link between the use of statins and muscular and renal adverse events, health care professionals and patients need to be educated regarding the potential association of muscular and renal adverse events associated with use of statins.
- The identification of potential signals in this study warrants future pharmacoepidemiologic studies to investigate the association between muscular and renal adverse events associated with statins in the US.

## CONCLUSION

- Potential signals for pitavastatin-associated muscular and renal adverse events were comparable to other statins in the US using FAERS.

## REFERENCES

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