

White Paper

Quantitative Evaluation of Safety of Statins

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Abstract

Introduction:

Statins have well-documented adverse effects related to two system organ classes (SOCs), musculoskeletal and renal. In this paper we wish to statistically compare adverse events (AEs) that belong to these two SOC classes across three Statins: Atorvastatin, Rosuvastatin and Simvastatin, using the United States Food and Drug Administration (US FDA) adverse events reporting system (AERS) data from the first quarter of 2004 through the first quarter of 2009. The objective is to investigate if the reported incidence of AEs in each of the 2 SOC classes varies across the 3 Statins. In order to do this comparison, we select one widely used brand of each of the 3 Statins. We evaluate statistical significance of differences in reported incidences using a linear model.

Methods:

For a fixed drug fixed adverse event combination we estimate the proportional reporting ratio (PRR) for each quarter between Q1 2004 and Q1 2009. Since the asymptotic distribution of log (PRR) is normal we use a linear model to assess if musculoskeletal and renal adverse events differ across the three Statins.

Conclusions:

Musculoskeletal adverse events that were reported in the AERS database were significantly higher among people using Rosuvastatin than those using Atorvastatin (PRR=6.82 v/s 4.25; $p < 0.0001$) and were somewhat significantly higher among people using Simvastatin than those using Atorvastatin (PRR=5.53 v/s 4.25; $p=0.055$). Overall reported incidence of renal adverse events was not also was significantly higher with Rosuvastatin (PRR = 1.27) than with Atrovastatin (PRR = 0.78; $p < 0.0001$) and was also significantly higher with Simvastatin (PRR = 1.36) than with Atorvastatin (PRR = 0.78; $p < 0.0001$).

Keywords:

Proportional reporting ratio, Linear model, Statins

1. Introduction

Statins are a very well known class of hypolipidemic drugs. These are the most potent cholesterol-lowering agents. Statins help in reducing low-density lipoproteins (LDL), commonly known as ‘bad cholesterol’, thus effectively decreasing the risk of cardiac events (e.g. heart attack, sudden cardiac death etc.). There are many drugs available in this class, Atorvastatin, Lovastatin, Pravastatin, Simvastatin etc. Some Statins are more popular than others, but overall, Statins are very widely prescribed world-wide for hypercholesterolemia.

Statins also have known adverse effects primarily related to musculoskeletal and renal organ classes. Possibility of these adverse events (AEs) is well documented in the labels and in the literature. Some of the common musculoskeletal events reported are myalgia, myopathy, rhabdomyolysis, increased blood creatinine etc. Some Statins have been withdrawn from the market in the past when their usage was associated with an increased incidence of serious adverse events. For example, Baycol was withdrawn from the market in August, 2001 due to risk of serious adverse effects.

In this article, we compare three of the most widely used Statins with respect to adverse events reported against these drugs. Here, we consider one widely used brand of each of three Statins - Atorvastatin, Simvastatin and Rosuvastatin and we statistically compare AEs related to musculoskeletal and renal systems. We refer to the three brands as Drug A, Drug B and Drug C while we present the results. We use the United States Food and Drug Administration (US FDA) Adverse Event Reporting System (AERS) data from Q1 2004 through Q1 2009. The objective of this article is to investigate if there is a statistically significant difference between these three Statins, for AEs related to the musculoskeletal system and for AEs related to

the renal system. We did not find results in the signal detection literature that were based on statistical modeling and significance tests for Proportional Reporting Ratios (PRRs), or any of the other statistical measures of signal detection. In this paper we have modeled the PRRs and concluded statistical significance from these models. The analysis and comparison of the data on statins serves as an illustration of the statistical modeling of PRRs.

The organization of the article is as follows: Section 2 describes the methods, the results are in Section 3 and the discussion of results is in Section 4. We state the conclusions in Section 5.

2. Materials and Methods

For a fixed drug and for a fixed adverse event (AE) combination, it is possible to construct a 2x2 contingency table as in Table 1.

Table 1: 2x2 contingency table for a particular drug and a particular AE

DRUG \ AE	AE under study	Other AEs
Drug under study	<i>a</i>	<i>b</i>
Other drugs	<i>c</i>	<i>d</i>

The fundamental idea behind safety data mining is to find the significance of the count ‘*a*’, since the total number of drug-event combinations ($N = a + b + c + d$) is large. Statistical interpretation of this objective is to find if the attribute DRUG is independent of the attribute AE.

The simplest and most widely used measure is known as Proportional Reporting Ratio (*PRR*) (EV-EWG, 2006). Given a 2x2 contingency table, *PRR* can be calculated from using the following expression:

$$PRR = \frac{a/(a+b)}{c/(c+d)}$$

The interpretation of *PRR* is that it is the ratio of probability of occurrence of the AE while on the drug under study, to probability of occurrence while on any other drug. So a unit value of *PRR* will indicate independence of the two attributes and any *PRR* value greater than, say, 2, would possibly raise a concern. Also, natural logarithm of *PRR* values follows an asymptotically normal distribution as shown below (EV-EWG, 2006):

$$\ln(PRR) \xrightarrow{D} N\left(\ln(PRR_0), \left(\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}\right)\right) \quad (1)$$

where PRR_0 is the population mean of *PRR* values. We use this result to compare three different Statins with respect to musculoskeletal and renal adverse events.

From the FDA AERS data, we calculate *PRR* values for each quarter from Q1 2004 through Q1 2009 after pooling adverse events (Preferred Term – PT- level) related to musculoskeletal SOC and renal SOC. Then we compare the Statins for each SOC using a linear model as given below.

$$\ln(PRR) = \text{intercept} + \text{drug(soc)} + \text{quarter} + \text{error} \quad (2)$$

The focus of this analysis is to compare the effects due to the three Statins, nested within the two SOCs. The effect due to quarter is treated as a blocking factor. Tukey’s method is used to adjust for multiple comparisons while making pairwise statistical comparisons.

Two important assumptions of linear models are independence and normality of the error term. Normality assumption is supported by the result stated above. Moreover, since the total number

of drug-event combinations in the FDA AERS database is very high, the assumption of asymptotic normality for $\ln(PRR)$ values can be justified. There can be some dependence in *PRR* values over different quarters because of follow-up cases. Although this is likely to be negligible in comparison to the size of the database, we considered only the initial report in the database to avoid any dependence. Also, independence of the drug effects is supported by the assumption that the chance of the same individual taking more than one Statin at any given time is low. Residual diagnostics are used to test the assumptions of normality and independence of errors.

3. Data Analysis

In this section, we present the results of the data analysis based on the US FDA AERS data from Q1 2004 through Q1 2009. In all our analysis, we considered Individual Safety Reports (ISR) and only if they were initial reports. The following PTs were included in the musculoskeletal SOC and the renal SOC respectively:

Musculoskeletal SOC:

CPK abnormal, CPK increased, Musculoskeletal discomfort, Musculoskeletal pain, Myalgia, Polymyalgia, Abnormal muscle biopsy, Muscle atrophy, Muscle disorder, Increased muscle enzyme, Muscle fatigue, Muscle injury, Muscle necrosis, Muscular weakness, Abnormal electromyogram, Acquired mitochondrial myopathy, Mitochondrial, Myopathy, Myoglobin blood, Increased blood myoglobin, Urine myoglobin, Presence of urine myoglobin, Myoglobinuria, Toxic myopathy, Myositis, Rhabdomyolysis.

Renal SOC:

Abnormal Blood creatine, Decreased creatinine renal clearance, Renal tubular acidosis, Renal tubular necrosis, Acute renal failure, Renal failure, Renal tubular disorder, Chronic renal failure, Abnormal renal function test, Hepatorenal failure, Interstitial nephritis, Tubulointerstitial nephritis, Nephritis, Allergic nephritis, Increased blood creatinine, Abnormal blood creatinine, Hypercreatininaemia, , nephropathy toxic, Nephrosclerosis, and Nephropathy.

US FDA AERS data were systematically reviewed for type of Statin and the chosen brands for each Statin, i.e., for Drugs A, B and C, and for related adverse events. A total of 1,263,828 records were systematically reviewed. In these 25,085 patients were on Drug A (Atrovastatin), 12,484 were taking Drug B (Simvastatin) and 13,523 on Drug C (Rosuvastatin). Overall 3,853,193 adverse events were reported. Of these 36,627 (0.95%) were musculoskeletal, 44,630(1.16%) were renal and other SOC's were 3,771,936 (97.89%). Table 2 gives the distribution of musculoskeletal and renal adverse events by Drug.

(Simvastatin) v/s Drug C (Rosuvastatin) ($p = 0.208$). But patients taking Drug C (Rosuvastatin) had reported significantly higher musculoskeletal events compared to Drug A (Atorvastatin) ($p < 0.0001$) and patients taking Drug B (Simvastatin) also reported somewhat higher musculoskeletal AEs than patients taking Drug B ($p=0.055$). The estimated PRRs of renal adverse events by three Statins, Drug A (Atorvastatin), Drug B (Simvastatin) and Drug C (Rosuvastatin) were 0.78 (95% CI: 0.69, 0.89), 1.36 (95% CI: 1.2, 1.55) and 1.27 (95% CI: 1.12, 1.45). Renal AEs were not significantly different among patients taking Drug B (Simvastatin) v/s Drug C (Rosuvastatin) ($p > 0.97$). Patients on Drug A (Atorvastatin) had significantly lower PRR compared to those on Drug B (Simvastatin) ($p < 0.0001$) or those on Drug C (Rosuvastatin) ($p < 0.0001$).

Moreover, the data also indicated that musculoskeletal events had a higher reported incidence in the database than renal events, overall across all 3 brands of statins, as well as within each brand (all p -values < 0.0001).

Table 2: Distribution of adverse events by Drug

Adverse Event	Drug A (Atorvastatin)	Drug B (Simvastatin)	Drug C (Rosuvastatin).	Total
Musculoskeletal	3,785 (3.9%/43.7%)	2,277(5.2%/26.3%)	2,609(6.9%/30.1%)	8,671
Renal	1,083 (1.1%/41.3%)	898(2.0%/34.2%)	642(1.7%/24.5%)	2,623
Other	91,373(94.9%/54.8%)	40,885(92.8%/24.5%)	34,437(91.4%/20.7%)	166,695
Total	87,346	42,981	31,921	177,989

Using the model in equation (2) there was an evidence of presence of nested drug effect ($p < 0.0001$). Hence we further performed pair-wise drug comparisons within each SOC. The estimated PRRs of musculoskeletal adverse events for the three Statins for Drug A (Atorvastatin), Drug B (Simvastatin) and Drug C (Rosuvastatin) respectively were 4.25 (95% CI: 3.74, 4.83), 5.53 (95% CI: 4.86, 6.29) and 6.82 (95% CI: 6.0, 7.76). Musculoskeletal AEs were not different among patients taking Drug B

The inferences presented here are adjusted for multiple comparisons using Tukey's method after the nested model was fitted to the data.

Residual diagnostics were performed to test the assumptions of normality and independence. Both these assumptions were very well supported by the data.

4. Conclusions

Occurrence of musculoskeletal adverse events, as reported in the FDA AERS database and as measured by PRR, was significantly higher among people using Drug C (Rosuvastatin) than Drug A (Atorvastatin) (6.82 v/s 4.25; $p < 0.0001$) and also somewhat significantly higher among people using Drug B (Simvastatin) than Drug A (Atorvastatin) (5.53 v/s 4.25; $p=0.055$). Renal adverse events were reported to be significantly lower due to Drug A (Atorvastatin) (PRR = 0.78) compared to Drug B (Simvastatin) (PRR = 1.36; $p < 0.0001$) and also compared to Drug C (Rosuvastatin) (PRR = 1.27; $p < 0.0001$). However, upper limits of the confidence intervals for PRRs for renal adverse events for all 3 drugs were less than 2.0. Hence pairwise comparison of renal AEs across the drugs may not be meaningful from a clinical perspective.

5. Discussion

When pooled across relevant PTs to make up the Musculoskeletal and Renal SOCs, these data indicate an overall safety profile with respect to these two SOCs for Atorvastatin that is better relative to the overall safety profile for both Simvastatin and Rosuvastatin. Moreover, the data also indicate an increased association of all 3 statins (jointly and individually) with adverse events comprising the musculoskeletal SOC as compared with adverse events comprising the renal SOC.

A highlight of this paper is that statistical modeling and significance testing of a commonly used measure of safety signals (PRR) is carried out. The models fit the data well and the assumptions of the model were verified to hold, making the statistical inferences reliable and fairly robust.

We used PRR since it is the most commonly used quantitative measure in signal detection. We intend to study statistical model-based inference for other measures of signal strength in the future (Ref: Hauben M, Zhou X, 2003).

These results are based on one commonly used brand of each of the 3 statins and are based on 21 quarters of data extracted from the FDA AERS database, and have to be interpreted in the limited context of the data they are based on.

Moreover, we need to acknowledge that medical relevance is critical in signal detection and is critical for meaningful interpretation of statistical significance. In order to comment on the medical significance, an in-depth analysis would have to be carried out of the data from which the adverse event reports are generated. This is not possible for us to do, on the basis of the limited data that are available in the AERS public domain. However, this would be the next step required to complete the analysis and interpretation of the statistical results.

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