Comparison of Rhabdomyolysis Associated With Sacubitril/valsartan-related Drug-drug Interactions by Individual Statins in an Adverse Event Reporting System

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Research Article

Keywords: sacubitril/valsartan, statin, rhabdomyolysis, organic anion-transporting polypeptide1B1, inhibiter

DOI: https://doi.org/10.21203/rs.3.rs-265192/v1

Abstract

Background

Sacubitril/valsartan was approved in Japan recently. Sacubitril is an inhibitor of organic anion-transporting polypeptide (OATP) 1B1 and 1B3. In Japan, sacubitril/valsartan product labeling indicates that it should be cautiously co-administered with atorvastatin due to drug-drug interactions (DDIs). However, all statins are the substrates of OATP1B1 and/or 1B3. Therefore, we should be cautious about DDIs between sacubitril/valsartan and all other statins.

Objective

To evaluate the association between rhabdomyolysis and concomitant association of sacubitril/valsartan with atorvastatin and all other statins.

Methods

Case reports from the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) from 2015 to Q4/2020 were used. All FAERS reports on sacubitril/valsartan were captured through a structured analysis. We compared the proportion of cases reporting the adverse events associated with rhabdomyolysis and the concomitant use of sacubitril/valsartan and atorvastatin to those with sacubitril/valsartan and all other statins.

Results

Among 10,940 case reports on sacubitril/valsartan, compared with all other drugs, statin users were associated with increased rhabdomyolysis (reporting odds ratio =4.54[2.62-7.87]). However, compared with all other statins, atorvastatin was not associated with increased rhabdomyolysis.

Conclusions

We suggest that the co-administration of sacubitril/valsartan with atorvastatin as well as other statins should be carefully managed as it may induce rhabdomyolysis.

Introduction

Rhabdomyolysis is a clinical syndrome caused due to extensive damage to the skeletal muscles, leading to life-threatening consequences, such as acute renal failure, cardiav arrhythmia, and hyperthermia [1]. The characteristic presentation of rhabdomyolysis includes a series of muscle pain, weakness, and dark colored urine, although all three does not always occur in a single patient. A variety of causes of muscle damage are known, and one of the most common causes is administration of drugs, such as, statins.

Recently, Faber et al. reported the incidence of rhabdomyolysis after coadministration of statin atorvastatin and sacubitril/valsartan [2]. Sacubitril/valsartan is a combination of neprilysin inhibitor and

an angiotensin II receptor blocker (ARB), which decreases the risk of hospitalization and cardiovascular death in patients with congestive heart failure (CHF). Coadministration of statins and sacubitril/valsartan is not rare, since patients with CHF commonly experience cardiovascular disease complications. Statins are widely used as the core therapy for the management of dyslipidemia, including primary and secondary prevention of cardiovascular diseases. Sacubitril/valsartan was approved by the Food and Drug Administration (FDA) in 2015 in the United States (U.S.) and by the Pharmaceuticals and Medical Devices Agency (PMDA) in 2020 August, in JAPAN.

Sacubitril/valsartan product labeling in Japan indicates that precautions should be taken for the coadministration of atorvastatin due to increased atorvastatin concentration induced by drug-drug interaction. Sacubitril is an *in vitro* inhibitor of organic anion-transporting polypeptide (OATP) 1B1 and 1B3. However, all statins are the substrates of OATP1B1 and/or 1B3. Christensen et al. reported that there is potential interaction between individual statins and clarithromycin, known as OATP1B1 and/or 1B3 inhibitors, and a strong CYP3A4 inhibitor [3]. They indicated that clarithromycin substantially increases the systemic exposure to simvastatin and lovastatin (>5-fold increase in area under the plasma concentration-time curve [AUC]), moderately increase the AUCs of atorvastatin and pitavastatin (2- to 4-fold AUC increase), and slightly increase the exposure to pravastatin, while exerting little effect on fluvastatin or rosuvastatin [3]. Therefore, we consider that the health providers should also be careful in prescribing statins other than atorvastatin to patients with CHF. We hypothesized this because all statins are the substrates of OATP1B1, and adverse events due to the co-administration of atorvastatin and sacubitril/valsartan may not be detected compared to that of all other statins and sacubitril/valsartan.

Method

Case reports from the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) from 2015 to Q4/2020 were used. As Japanese Adverse Drug Event Report (JADER) is included few data regard sacuvitril/valsartan due to be approved very recent in JAPAN, we used FAERS database that is approved in 2015 in the U.S. instead of JADER database. All FAERS reports on sacubitril/valsartan were captured through a structured analysis. These reports were stratified to those wherein an outcome of "rhabdomyolysis" or "myopathy" versus all other reactions based on the Medical Dictionary for Regulatory Activities (MedDRA) definitions was reported. All other statins were defined as statins other than atorvastatin. Statins were identified in the same case report as a source of binary exposure (yes/no).

We calculated the reporting odds ratios (RORs) and 95% confidence intervals (95% CI) using the 2 × 2 exposure-outcome contingency tables to assess the disproportionality of rhabdomyolysis reports between the exposed and unexposed groups (Fig. 1) [4]. A common interpretation of a significant effect is based on the ROR's lower 95% CI of ≥1.0. Detailed calculation of ROR was discussed by Poluzzi et al [4]. We compared statins with all other drugs. Additionally, we stratified the data on the basis of the type of statin and compared atorvastatin with all other statins. Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Results

A total of 10,940 sacubitril/valsartan cases were identified, out of which 3850 cases (35.2 %) involved statins. The most common concomitant statin used was atorvastatin (2163 cases, 19.8%). Additionally, simvastatin, rosuvastatin, pravastatin, lovastatin, pitavastatin, and fluvastatin accounted for 649 (5.9%), 623 (5.7%), 289 (2.6%), 81 (0.7%), 33 (0.3%), and 12 (0.1%) cases, respectively. Among statin users (1.1% of reports), the lower 95% CI indicated a significant association with all other drugs and rhabdomyolysis (ROR=4.54[2.62-7.87], Table 1). Conversely, among atorvastatin users (1.2% of reports), the lower 95% CI did not indicate a significant association with all other statins and rhabdomyolysis (ROR=1.13[0.62-2.06], Table 1).

Discussion

We suggest that statins are susceptible to sacubitrl/valsartan drug-drug interactions. Moreover, these results indicate a similar association between the use of statins and rhabdomyolysis among sacubitril/valsartan users, which is independent to the type of statin administered.

The activity of OATP1B1 is affected due to genetic polymorphism, as approximately 15%-20% of Caucasians, 10%-15% of Asians, and 2% of African Americans carry at least one low-activity SLCO1B1 allele [5]. Although our results are based on the U.S. FAERS database, the activity of OATP1B1 in Caucasians is identified to be similar to that in Asians. Therefore, we consider that Japanese population might experience rhabdomyolysis due to the co-administration of statins and sacubitril/valsartan.

In a literature search regarding the drug interactions between sacubitril/valsartan and statins, we identified two reports of rhabdomyolysis with statins [2, 6]. Sacubitril is an OATP inhibitor, and a moderate interaction between sacubitril and atorvastatin, with a 1.7-fold increase in Cmax and a 1.3-fold increase in AUC was predicted based on a physiological pharmacokinetic model [7]. Additionally, a recent study showed that the co-administration of sacubitril/valsartan with atorvastatin led to a two-fold increase in the maximum concentration (Cmax) of atorvastatin and its metabolites [8]. Moreover, rosuvastatin exhibited a slightly higher affinity for OAPT1B1 than atorvastatin [9]. Therefore, the drug-drug interaction would be higher upon the co-administration of sacubitril and rosuvastatin. In a recent study, AUC of rosuvastatin was shown to be increased by 11-fold upon co-administration with sacubitril/valsartan in rats [10]. Therefore, we suggest that not only atorvastatin but also all other statins might be responsible for inducing rhabdomyolysis caused due to drug-drug interactions.

However, our study has several limitations. FAERS case reports do not include a denominator of medication users and may not be used to report the rates between the groups. FAERS data are spontaneously reported and subject to reporting biases associated with the public knowledge on safety issues, release of new medications, or masking effects due to an imbalance in event reporting. Reported reactions or medications in the case reports are not further adjudicated. Therefore, to reduce the potential bias, we only used statins. Other important factors, such as infection, excessive exercise, and excessive

alcohol consumption, are not routinely captured in FAERS, and thus, may influence the induction of rhabdomyolysis.

Implications

Atorvastatin and other statins are susceptible to drug-drug interactions. This study provides the evidence based on FAERS that the co-administration of OATP1B1-inhibiting sacubitril/valsartan with atorvastatin as well as other statins should be carefully managed as it may induce rhabdomyolysis.

Conclusion

We suggest that the drug-drug interaction between atorvastatin as well as other statins and sacubitril/valsartan might significantly increase the plasma concentration of individual statins. Sacubitril/valsartan has already been included in the treatment guidelines for CHF. Therefore, particular attention should be paid when treating the patients with CHF, who are increasingly administered with this combination of drugs.

Declarations

Funding sources: No special funding was received for this study.

Conflict of interests: The authors declare no conflict of interest.

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Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.