

Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors Induced Neurocognitive Disorder: A Pharmacovigilance Study by Analyzing the Data from the U.S. FDA Adverse Event Reporting System

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Abstract

Purpose

The neurocognitive disorder is a rare adverse event associated with Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors in the randomized controlled trial (RCTs), there was limited evidence to prove their relation. This study aimed to assessing their association by detecting adverse signal in the FDA Adverse Event Reporting System (FAERS).

Methods

The disproportionality analysis was conducted to detect the potential adverse signal between neurocognitive disorders and PCSK9 inhibitors. The adverse event reports from the first quarter of 2004 to the second quarter of 2020 were extracted from the FAERS database.

Results

There were 81,272 adverse reports correlated with the usage of the PCSK9 inhibitors, of which 152 reports corresponded with our inclusion criteria. Among them, there were 106 and 46 neurocognitive disorder reports related to the usage of Evolocumab and Alirocumab, respectively. The total ROR value presented negative disproportionality, however, Alirocumab has generated a positive signal with a higher ROR value in comparison with Evolocumab. Moreover, there were 61.19% of adverse reports were submitted by healthcare professionals. As for the outcome events, 7.79% of patients had initial or prolonged hospitalization and 3.90% suffered a disability.

Conclusion

The pharmacovigilance research helps to find out more about PCSK9 inhibitor-related neurocognitive disorders. Although the positive signal was identified in Alirocumab in this study, it still required further research to prove the association between neurocognitive disorder and PCSK9 inhibitors. In addition, the tenable mechanism should be explored, which can improve the insight of this neotype lipid-lowering medicine.

Key Points

- This study used FAERS as the data source to detect signals between PCSK9 inhibitors and neurocognitive adverse events (AEs).
- With the application of disproportionality analysis, it is the first time that the AEs signal of neurocognitive disorder associated with the usage of Alirocumab is identified in the post-marketing stage.
- This study presented the interpretation of the false positive signal and negative signal in disproportion analysis.

- Patients administered Alirocumab as lipid-lowering therapy require surveillance for the neurocognitive AEs.
- The analysis of adverse outcomes provided useful suggestions for the regimen of lipid-lowering therapy in the clinic.

1. Introduction

The Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) is a protein that can affect normal cholesterol homeostasis regulation. It reduces plasma low-density lipoprotein receptor (LDL-R) levels by binding to and subsequently degrading them[1, 2]. This will lead to reduced metabolism of low-density lipoprotein cholesterol (LDL-C) thus inducing hypercholesterolemia[3], then developing to atherosclerosis. PCSK9 inhibitor can interfere with this process, resulting in higher LDLR expression as well as lower plasma LDL levels. Evolocumab (Repatha) and Alirocumab (Praluent) are two PCSK9 inhibitors approved by the U.S. FDA as a cholesterol-lowering agent in 2015. Later, both of them were proved for their effective performance in the management of atherosclerotic cardiovascular diseases (ASCVD) patients.

With the lipid management guidelines updating, lipid-lowering therapy has become extremely vital for ASCVD patient treatment[4]. However, previous reports showed that some neurocognitive impairment cases were possibly associated with first-class medication, the statin. Given the effect of PCSK9 on cholesterol levels and the importance of cholesterol regulation, this is no doubt raised the concern about the PCSK9 inhibitors-related neuro-dysfunction[5, 6]. Neurocognitive disorder would gradually develop into dementia. It would become 'Alzheimer' in some severe cases. Most of the time, it is commonly diagnosed among senior citizens over 65 years old, which caused great burden for patient family and healthcare staff. Previous research surmised that that 115.4 million people would suffer from this disease by 2050[7][8]. To lower the occurrence of this horrible adverse event induced by a lipid-lowering medicine, FDA had urgently issued an instruction about the surveillance for PCSK9 inhibitors in 2014, but without any specific measures to assess this kind of side-effect.

To minimize the risk of medicinal accidents in the clinic, pharmacovigilance is mainly charged to identify the potential hazards or risks associated with medicine and other pharmaceutical products. It relies on a mature system is to monitor the safety of post-marketing medicines[9, 10], which including collection, detection, assessment, surveillance, and prevention of adverse events or adverse drug interactions. Due to the convenience of accessing comprehensive information, the spontaneous reporting system database is one of the main resources for pharmacovigilance studies. For example, the basic information of the patient, the usage of the drug, and detailed information about the adverse events[11]. Since some rare adverse events were hardly captured in the clinic trials, surveillance program for post-marketing medicine is particularly important for neotype drugs or long-term medicinal therapy. This is because some unexpected adverse events only occur after a large number of people receive the medicine, or the drug is being used for a longer period. Furthermore, the long-term monitoring activities are beneficial to delivering an objective appraisal of therapeutical effectiveness and long-term safety.

In recent years, some research was conducted to explore the correlation between PCSK9 inhibitors and neurocognitive disorder[12, 13]. However, there is a limited number of real-world based studies related to this subject, and the existing argument is that whether the occurrence of the neurocognitive disorder is the result of the usage of PCSK9 inhibitors. In addition, a tenable mechanism of PCSK9 inhibitors inducing neurocognitive dysfunction is still unknown. Here, we conducted this pharmacovigilance study with data retrieved from the spontaneous reports of the FDA Adverse Event Reporting System (FAERS) to supplement existing insufficient PCSK9 inhibitor usage information and provide evidence-based data for its usage and potential specific adverse effect in clinical practice.

2. Methods

2.1. Data Sources.

A retrospective pharmacovigilance study was performed by retrieving spontaneous reports related to neurocognitive disorder induced by PCSK-9 inhibitors during the first quarter of 2004 to the second quarter of 2020 in the FAERS database which is a highly reliable program supported by the FDA for the surveillance of post-marketing drugs safety. FAERS is the largest voluntary reporting database, which records substantial data including demographic information (DEMO), patient outcomes (OUTC), drug information (DRUG), adverse event (REAC), therapy start dates and end dates for reported drugs (THER), and indications for use (INDI). Healthcare professionals and consumers were the main reporting group, who can spontaneously submit adverse events resulting from medication error reports, drug interaction, and product quality complaints.

A total of 14,570,082 reports from the FAERS database and excluded duplicated records according to the FDA's recommendations by selecting the latest FDA_DT when the CASEID and FDA_DT were the same. We ultimately included 12,198,404 reports for signal detection.

2.2. Adverse Event and Drug Identification.

Adverse events investigation was based on the summary of both previous research and literature review. The FAERS database was used to collect voluntarily submitted PCSK9 inhibitor treatments in association with neurocognitive disorder reports by inputting the following preferred terms from the Medical Dictionary for Regulatory Activities Terminology (MedDRA, version 23.1): cognitive disorder[code:10057668]. The MICROMEDEX (Index Nominum) was used as a dictionary of PCSK9 inhibitors (Table 1).

Table 1
Generic name and brand name of
PCSK9 inhibitors

Generic name	Brand name
Alirocumab	PRALUENT®
Evolocumab	REPATHA®

2.3. Signal detection.

Reporting Odds Ratio (ROR) is one of the frequentist algorithms for data mining, which has been commonly operated in pharmacovigilance studies with an important performance[14, 15]. The algorithm of ROR is defined as below[16]:

$$\text{ROR} = (a/b)/(c/d)$$

$$95\% \text{ CI} = e^{\ln(\text{ROR}) \pm 1.96(1/a+1/b+1/c+1/d)^{0.5}}$$

Positive signal criteria: 95%CI>1, N≥2

In the first equation, **a** is the total number of reports of the target medicine associated with the neurocognitive disorder. **b** is the number of reports representing the other lipid-lowering medicine inducing neurocognitive disorder, except PCSK9 inhibitor. **c** is the number of reports containing other adverse events caused by PCSK9 inhibitor but without the neurocognitive disorder. **d** is the number of reports containing neither PCSK9 inhibitor nor the neurocognitive disorder. The second equation is the 95% confidence interval (95% CI), **e** is the natural constant, and **ln** is the natural logarithm.

Our study applied the above equations to calculate both ROR and 95% CI. The value of ROR was utilized to assess the correlation between two PCSK9 inhibitors and neurocognitive disorder, respectively. It can be defined that the positive signal is identified, if the lower limit of the two sides of the 95% CI is over 1, with the total reports number (N) should be more than 2.

2.4. Statistical Analysis.

The clinical features of patients with PCSK9 inhibitors associated with the neurocognitive disorder were summarized by descriptive analysis. Since the data were not normally distributed, the onset time of cognitive dysfunction induced by different PCSK9 inhibitor therapies was compared by nonparametric tests (the Mann-Whitney test for dichotomous variables and the Kruskal-Wallis test for >2 subgroups of respondents). Pearson's chi-square test or Fisher's exact test was utilized to compare the disability and mortality rate of the neurocognitive disorder in patients receiving different PCSK9 inhibitors. Statistical significance was declared at P < 0:05 with 95% confidence intervals. Both data mining and statistical analysis were estimated by SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Result

Within the study period, 81,272 adverse reports were related to PCSK9 inhibitor treatments, and 26,843 related to neurocognitive disorders. Through data mining technology, 152 reports correspond with our inclusion criteria. In Table 2, it demonstrates the specific demographic and clinical characteristics of these patients as well as some important information of these reports. In terms of the gender composition, the report number of neurocognitive disorders in both males and females were quite similar, with the percentage of 47.37% and 48.03%, respectively. The range of age was from 0 to 87 years old, the proportion of patients with the age at 45 to 64 presented the highest percentage, except the unknown age patients. In terms of the reporters, the healthcare professionals were the main group who submitted the reports. Over ninety percent of reports were reported from North America. The Other Serious (Important Medical Event) took up 87.01% of the whole outcome events. No death event was reported.

Table 2
Detail information of neurocognitive disorder reports.

Characteristics	Alirocumab n (%)	Evolocumab n (%)	Total n (%)
Patient's average weight (kg)	77.71	86.00	81.85
Patient's age			
<18	1	0	1 (0.66)
18-44	2	0	2 (1.32)
45-64	12	29	41 (26.97)
65-74	9	25	34(22.37)
75-84	4	20	24(15.79)
>85	2	1	3(1.97)
Unknown	16	31	47(30.92)
Patient's sex			
F	19 (41.3%)	54 (50.94%)	73(48.03)
M	26 (56.52%)	46 (43.4%)	72(47.37)
Unknown	1 (2.17%)	6 (5.66%)	7(4.61)
Reporting country			
Australia	1	1	2 (1.32)
Brazil	0	1	1 (0.66)
Canada	1	0	1 (0.66)
Germany	0	4	4 (2.63)
Italy	0	1	1 (0.66)
Netherlands	1	0	1 (0.66)
Singapore	0	1	1 (0.66)
Spain	1	0	1 (0.66)
Switzerland	0	2	2 (1.32)
UK	0	1	1 (0.66)
USA	42	95	137 (90.13)
n is the number of the reports.			

Characteristics	Alirocumab n (%)	Evolocumab n (%)	Total n (%)
Indication			
Arteriosclerosis coronary artery	3	2	5 (3.60)
Dyslipidemia	10	27	37 (26.62)
Cardiovascular disorder	1	3	4 (2.88)
Hypercholesterolemia	6	18	24 (17.27)
Hyperlipidemia	10	18	28 (20.14)
Peripheral arterial occlusive disease	0	1	1 (0.72)
Product used for unknown indication	0	39	39 (28.06)
Others	1	0	1 (0.72)
Type of reporter			
Consumer	28	30	58 (38.16)
Other health-professional	6	15	21 (13.82)
Pharmacist	2	2	4 (2.63)
Physician	9	59	68 (44.74)
Unknown	1	0	1 (0.66)
Onset time of adverse event			
0-30 days	3	8	11
30-60 days	2	1	3
60-90 days	0	1	1
>90 days	0	1	1
Outcomes of event			
Disability	2	1	3 (3.90)
Hospitalization-Initial or Prolonged	3	3	6 (7.79)
Life-Threatening	0	1	1 (1.30)
Other Serious (Important Medical Event)	8	59	67 (87.01)
n is the number of the reports.			

In total, there were 152 neurocognitive disorder reports related to PCSK9 inhibitor with the ROR value at 0.85. 106 reports were associated with Evolocumab, while 46 were in correlation with Alirocumab usage. According to the criteria of disproportional signal detection, the positive signal was exclusively identified in the patients who received Alirocumab (Table 3).

Table 3
The ROR value of PCSK9 inhibitors.

Drug name	n	ROR (95% two-sided CI)
Total PCSK9 inhibitors	152	0.85 (0.72 ,1.00)
Alirocumab	46	1.41 (1.06 ,1.89)
Evolocumab	106	0.72 (0.60 ,0.88)

n is the number of neurocognitive disorder reports. ROR is the reporting odds ratio, the value in the parentheses represents the two sides of 95% confidence interval.

The onset time of the adverse event under each medication therapy PCSK9 inhibitor was also evaluated. It was defined as the time interval between the date patients initiated injecting PCSK9 inhibitors and the day that neurocognitive disorder onset date. The potential database errors and reporting errors, such as the start date earlier than the onset date were excluded. As a result, 16 valid data indicated that the neurocognitive disorder had occurred at the scale of 0 to 618 days, with the median at 1.5 days.

4. Discussion

In this study, disproportionality analysis revealed that Alirocumab may correlate with the neurocognitive disorder due to the presenting positive signal, while the total PCSK9 inhibitors and Evolocumab presented a negative signal with a weak correlation. From the report system, we retrieved 77 neurocognitive disorder outcome events which should pay more attention to the clinic, including primary and long-term hospitalization (7.79%), disability (3.90%) and life-threatening (1.30%). In addition, the origin of reports was summarized to accumulate more adverse event information of PCSK9 inhibitors in the real world.

Disproportionality signal can help to establish a new potentially causal association between PCSK9 inhibitors and neurocognitive disorder[17]. Alirocumab was highly associated with the neurocognitive disorder, but Evolocumab was not related. This result is consistent with the finding obtained in two previous RCTs. The ODYSSEY LONG TERM trial indicated that Alirocumab caused a higher ratio of neurocognitive disorder occurrence than placebo[6]. Another prospective study assessed the cognitive function of the patients, EBBINGHAUS trial concluded that there was no significant difference between the Evolocumab and placebo[18]. In two large meta-analyses, Khan et al. (2016) and Lipinski et al. (2015) found that there was an increased occurrence of neurocognitive disorder after the usage of PCSK9 inhibitors[5, 19]. Although their result further supports the idea that there is a signal toward PCSK9 inhibitors associated with the neurocognitive disorder, they did not identify which PCSK9 inhibitor existed the potential relation with neurocognitive impairment. Our study is distinguishing from the anterior RCTs

and meta-analysis study because we had comprehensively applied the pharmacovigilance study method to detect the drug-event signal. Thus, a larger amount of data can be obtained to reveal the hidden relationship between the adverse event and PCSK9 inhibitors. For example, the meta-analysis conducted by Lipinski et al. enrolled 17 RCTs, 13,083 patients participated, whereas, this study included 12,198,404 reports, which is much more than these four mentioned studies. Consequently, the sufficient real-world datasets can transform into valuable evidence to improve the insight of the medication effect.

However, there would be a concern that the signal of the Alirocumab report was a false positive. Alirocumab may not have any association with the neurocognitive disorder as Karatasakis A. et al. studied it[13]. Their finding was based on a meta-analysis, which involved 21 RCTs including 42,668 patients who participated in analyzing neurocognitive adverse events. Some potential biases may lead to an alpha error in our study. For example, PCSK9 inhibitors were exclusively prescribed for very-high risk ASCVD patients for managing their LDL-C level, which caused the channelling bias. In addition, the notoriety bias was existed, because some stimulating reports were raised after the FDA had issued the surveillance. With the existence of the above bias, evaluating the false positive signal by a single study is impossible. But it can motivate the healthcare professionals to pay more attention to monitoring the neurocognitive dysfunction among the patients who received Alirocumab. The follow-up data and cognitive evaluation report are vital sources for case analysis then assessing the false positive signal. Moreover, the negative disproportion signal should not be interpreted as a safety endorsement[16, 17]. Although the signal of Evolocumab is negative, it cannot infer that neurocognitive disorder is unassociated with Evolocumab. Since disproportion analysis is only used for adverse signal detection and prioritization, it cannot identify the risk and mechanism of medicine. Therefore, establishing the causality of neurocognitive disorder and PCSK9 inhibitors should require more comprehensive evidence. Recent research proposed the mechanism that the neurocognitive adverse event may pose by sustained low LDL-C levels. While the treatment effect of PCSK9 inhibitor can promote the above process, thus neurocognitive dysfunction becomes the potential adverse event[12, 20]. Based on this mechanism and the disproportional analysis, it is necessary to keep vigilant for the usage of PCSK9 inhibitors in the clinic and record the effect. The collected data would further prove the causality of PCSK9 inhibitor and neurocognitive disorder.

From the traits of the report, neurocognitive adverse events occurred after a period of using PCSK9 inhibitors. We found that neurocognitive related events occurred among 5 patients within one year. This result matched those observed from Koren et al[21]. They reviewed the OSLER-1 trial including 12,251 patients, and 8 patients presented neurocognitive disorder in the first year after using Evolocumab. However, data related to the onset time of Alirocumab have remained absent because many RCTs did not demonstrate the detailed information of adverse event onset time. Although the sample size of onset time was limited in this study, we still calculated the median for analysis, however, less valuable information was obtained. By analyzing the age of the patient provides, we find that the neurocognitive disorder was concentrated in the age of 45 to 64 patients. Normally, dementia would occur among the patient who is over 65 years old, except the Frontotemporal dementia because it can induce onset earlier[7, 22]. In addition, around 60% of reports were submitted by the healthcare professionals, the

source of data was reliable. These reports may relate with the PCSK9 inhibition, but it lacks the follow-up data or the subsequent report. For example, whether the patients recovered after withdrawing the PCSK9 inhibitors. Therefore, it still requires more evidence.

Since PCSK9 inhibitor is pricy for patients, the potential adverse event possibly leads to the increasing of therapy cost, then patient life-quality would decrease. A systematic review concludes that although adverse events associated with PCSK9 inhibitors were rare in most outcome studies and RCTs, the severe events were still existing[23]. Another research based on the real-world experience[24] inferred that although the adverse effect did not interfere with the usage of PCSK9 inhibitors since it was rare, Gurgoze MT. et al. pointed out that balancing the long-term benefits and potential adverse events is a critical process. The rare adverse events should not be neglected, but the real-world data of PCSK9 inhibitors was limited. Thus, it is vital to collect more evidence of adverse events associated with PCSK9 inhibitor[24–26]. Here, we therefore advocate performing more drug pharmacovigilance programs for PCSK9 inhibitors, consequently, the awareness of those serious adverse effects among patients and clinicians will be enhanced, which is also beneficial for the patient to remain safe and reduce medical costs.

As real-world study is developed for post-approved drug surveillance, it performs differently from the RCTs in reflecting the real clinical treatment, especially for drug safety assessment[27, 28]. Since the real-world data is based on clinical observation, some rare but important clinical features can preserve as supplementary evidence to the pharmacovigilance study. Besides, real-world evidence also helps to provide a practical and persuasive clinical suggestions for healthcare professionals[27].

Although the recognition of the potential of big data analytics is rising, its application in pharmacovigilance research is still emerging. FAERS database might be a useful tool for pharmaceutical companies to collect related efficacy and safety information because the preserved data size and worldwide coverage of this database are conducive to provide robust evidence for the conduction of spontaneous reporting data analysis. Moreover, the substantial volume of data contributes to real-world study, in terms of saving the research cost and time compared with the RCTs[29, 30].

Data mining of the FAERS database can obtain the previously unknown, but clinically important drug and adverse events associations[31]. Since the valuable information comes from the raw data, the application of data mining technology is vital for the pharmacovigilance study. Establishing the association between the drug and adverse event is a complex process, the connection requires deep investigation, such as the inducement mechanism. A disproportional signal is a symbol to guild the researchers to find out the new objective. With the comprehensive and multifaceted study, drug safety can be reached to a higher level.

There were several limitations in this study. First, the subjectivity is the main factor in drug-related adverse event research[32]. As the FDA did not require the reporters should be an expert or professionals in pharmacovigilance activities, the quality of the adverse reports is particularly different. There might contain underreported or submitted with false and incomplete information. Second, the worldwide coverage of the FAERS may become a two-edged sword. It provides a substantial sample size, but the different reporting culture from different countries is another major source of heterogeneity, which affects

the quality of the reports as well. Third, the causal relationship between medication and the adverse event may not be consistent, because the report lacks relative evidence. Furthermore, the spontaneous reporting system cannot quantitatively measure the signals of neurocognitive disorder based on the total number of adverse reactions. It also cannot calculate the exact incidence of potential adverse events, the main reason is the spontaneous reporting system has insufficient exposure data, which corresponds to the denominator of incidence. Despite the above limitation, the FAERS database is still a reliable source of real-world data for the disproportional signal study. In the future pharmacovigilance study, the analysis for causality of PCSK9 inhibitor and neurocognitive disorder should be together with clinical follow-up and cognitive function evaluation.

5. Conclusion

In conclusion, we conducted the disproportional analysis between PCSK9 inhibitors and neurocognitive disorder in a number of real-world reports based on the FAERS database. Although a disproportional signal was detected, both Alirocumab and Evolocumab require further study to reassess the safety. Due to the usage of PCSK9 inhibitors is expected to rise in the clinic for the next few years, pharmacovigilance study is extremely necessary and vital for monitoring neurocognitive disorders. As the number of long-term follow-up reports increases, the collected real-world data will significantly increase the evidence quality. Furthermore, it will assist to facilitate the administration of PCSK9 inhibitors in the clinic.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. The ideas were created by Yang Hu and Ziyubai. Material preparation, data collection and analysis were performed by Yang Hu, Bin Zhao, Ziyu Bai, Xinyue Zhang and Tianxin Huang. The first draft of the manuscript was written by Tianxin Huang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Statement

The authors state that no ethical approval was needed.

Conflict of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Data Availability Statements

The data of patient's characteristics are come from the spontaneous reports of the FDA Adverse Event Reporting System (FAERS). The data that support the findings of this study are available from the corresponding author upon reasonable request.

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