SFDA SAFETY SIGNAL

"A signal is defined by the SFDA as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature"

25-07-2023

Saudi Food and Drug Authority (SFDA) – Safety Signal of Atorvastatin and the Risk of Erectile dysfunction

The Saudi Food and Drug Authority (SFDA) recommends all health care professionals to be aware of the safety signal of ***Erectile dysfunction*** *associated with the use of* ***Atorvastatin****. The signal has been originated as a result of routine pharmacovigilance monitoring activities.*

Introduction

Atorvastatin is a potent, orally available inhibitor of hepatic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the major rate-limiting enzyme in cholesterol synthesis. Like other members of its class (the "statins"), atorvastatin lowers total serum cholesterol and low density lipoprotein (LDL) concentrations, thereby reducing the risk of atherosclerosis and its complications – myocardial infarction and stroke. Atorvastatin was approved for use in the United States in 1996 and has become one of the most commonly prescribed drugs in America, with more than 50 million prescriptions filled yearly. The current primary indication for atorvastatin is the treatment of hypercholesterolemia in persons at high risk for coronary, cerebrovascular and peripheral artery disease. [1] Erectile dysfunction (ED), formerly termed impotence, is defined as the failure to achieve or maintain a rigid penile erection suitable for satisfactory sexual intercourse. [2] While no specific time period is part of this definition, some have suggested that the condition needs to persist for six months. It is a common condition in men aged over 40 years, with the prevalence increasing steeply with age and other co-morbidities.[3] The aim of this review is to evaluate the risk of Erectile dysfunction associated with the use of Atorvastatin and to suggest regulatory recommendations if required.

Methodology

Signal Detection team at SFDA performed a signal review using National Pharmacovigilance Center (NPC) database, and World Health Organization (WHO) database, VigiBase, with literature screening to retrieve all related information to assess the causality between Erectile dysfunction and Atorvastatin use. The search conducted on April 2023.

Results

Case Review: Signal detection team at SFDA have searched Saudi national database and WHO database to find individual case safety reports (ICSRs). Locally, there were 4 reported cases in Saudi Arabia, one of them assessed as possible association. The WHO database resulted in 615 global case-reports. [4] Author extracted the top 30 cases with highest completeness score (1.0) for further evaluation and application of WHO causality assessment criteria. Among them, 24 cases of erectile dysfunction were either probably or possibly linked to atorvastatin.

Datamining: The disproportionality of the observed and the expected reporting rate for drug/adverse drug reaction pair is estimated using information component (IC), a tool developed by WHO-UMC to measure the reporting ratio. Positive IC reflects higher statistical association while negative values indicates less statistical association. The IC result is (1.9) for this drug/ADR combination which reflects high statistical association. [5]

Literature:

On April 2023, the author searched for eligible publications using the terms "Atorvastatin" and "Erectile dysfunction". French Pharmacovigilance System Database, the case/non-case method was used to measure the disproportionality of combination between a statin and ED. Cases are defined as those reports corresponding to the ADR of interest (i.e. ED) and non-cases are all reports of ADRs other than that being studied. The study period was from 1 January 1985 to 31 December 2006, limited to males aged 13-80 years. Among the total of spontaneous reports selected (110 685), exposure to statins was identified in 4471 cases (4%), of which 51 reports (1.1%) concerned ED, whereas 431 (0.4%) cases of ED were found in the 106 214 reports without exposure to statins ($p < 0.0001$). The mean delay of onset of ED after starting statins, known for 19 cases, was 62 days (median 29 days). In 56.9% of cases, recovery occurred after withdrawal of statin, and rechallenge was positive in five cases. The association was statistically significant for all statins. [6]

Conclusion

The weighted cumulative evidence identified from assessed cases, literature and disproportionality analysis are sufficient to suggest causal association between Atorvastatin and Erectile dysfunction. Health care professionals and health regulators must be aware of the potential risk in drug recipients.

Report Adverse Drug Events (ADRs) to the SFDA

The SFDA urges both healthcare professionals and patients to continue reporting adverse drug reactions (ADRs) resulted from using any medications to the SFDA either online, by regular mail or by fax, using the following contact information:

National Pharmacovigilance Center (NPC)
Saudi Food and Drug Authority-Drug sector
4904 northern ring branch rd
Hittin District
Riyadh 13513 – 7148
Kingdom of Saudi Arabia
Toll free number: 19999
Email: NPC.Drug@sfda.gov.sa

References:

1- LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Atorvastatin. [Updated 2021 Dec 1]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548236/

2- Muneer A, Kalsi J, Nazareth I, Arya M. Erectile dysfunction. BMJ. 2014 Jan 27;348:g129.

3- Shamloul R, Ghanem H. Erectile dysfunction. Lancet. 2013 Jan 12;381(9861):153-65.

4- Vigilyze.who-umc.org. 2023. [online] Available at: https://vigilyze.who-umc.org/ [Accessed 28/03/2023].

5- World Health Organization WHO (2013). WHO-UMC system for standardised case causality assessment. Available at https://www.who.int/publications/m/item/WHO-causality-assessment [Accessed 28/03/2023].

6- Do C, Huyghe E, Lapeyre-Mestre M, Montastruc JL, Bagheri H. Statins and erectile dysfunction: results of a case/non-case study using the French Pharmacovigilance System Database. Drug Saf. 2009;32(7):591-7. doi: 10.2165/00002018-200932070-00005. PMID: 19530745.