Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Association of atorvastatin with the risk of hepatotoxicity: a pilot prescription sequence symmetry analysis

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

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Purpose: This study aimed to evaluate Atorvastatin (ATO)-associated hepatotoxicity using prescription sequence symmetry analysis (PSSA), based on a health insurance database of a Chinese population living in Jiangsu Province, China.

Methods: Patients prescribed ATO and hepatoprotective drugs in 2017 were identified, and the run-in period was determined based on the "waiting-time" distribution. Adjusted sequence ratio (ASR) and 95% confidence interval (95% CI) were calculated to estimate the risk of ATO-associated hepatotoxicity under different time intervals or based on gender and age stratification.

Results: A total of 2,549 patients, with 1,518 filling the ATO prescription first and 1,031 filling the ATO prescription second, were analyzed. After setting the run-in period as 30 days and the time interval as 15, 30, 60, 90, 120, and 180 days, the ASRs were 1.492 (95% CI: 1.367–1.652), 1.399 (95% CI: 1.308–1.508), 1.280 (95% CI: 1.213–1.357), 1.292 (95% CI: 1.234–1.356), 1.278 (95% CI: 1.226–1.336), and 1.274 (95% CI: 1.229–1.323), respectively. No significant difference was observed between different genders and ages (χ^2=0.161, P=0.688; χ^2=1.565, P=0.211, respectively).

Conclusion: This is the first study conducted in a real-world setting to evaluate the relationship between ATO and hepatotoxicity using the PSSA in a Chinese population. We found a 1.3- to 1.5-fold increase in risk of hepatotoxicity following ATO, with the greater risk occurring within the first 30 days of treatment.

Keywords: atorvastatin, hepatoprotective drug, prescription sequence symmetry analysis, health insurance database

Introduction

Atorvastatin (ATO) is one of the most widely prescribed drugs and statins in the world;[1] it decreases production of low-density lipoprotein (LDL) cholesterol by blocking the action of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase enzyme in the liver at the rate-limiting step of cholesterol biosynthesis.[2] Together with other statins, ATO has been commonly used for decades. Currently, ATO is proven to play other roles in decreasing the risk of heart failure,[3] cerebrovascular disease,[4] chronic subdural hematoma,[5] depression,[6] pancreatic cancer,[7] contrast-induced acute kidney injury,[8] rheumatoid arthritis,[9] and so on. Although ATO is safe and generally well tolerated across the range of its therapeutic dosage (10–80 mg/day);[10] it is associated with adverse effects, which are underrecognized as well as underreported.[11,12] Common adverse drug events (ADEs) or adverse drug

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http://doi.org/10.2147/TCRM.S204860

reactions (ADRs) for patients taking ATO include arthralgia, dyspepsia, diarrhea, nausea, nasopharyngitis, insomnia, urinary tract infection and pain in the extremities.[13] Additionally, ATO-associated myalgia,[11] hearing loss,[14] and hepatotoxicity[15,16] are often reported. Idiosyncratic liver injury associated with statins is rare but can be associated with severe outcomes,[17] and the research on this topic is incomplete but extremely necessary.[18]

Postmarketing surveillance is essential in order to protect patients against avoidable risks from medication.[19] Spontaneous reporting on ADRs is a quick method, but underreporting is a problem; intensive monitoring gives high quality data but is expensive.[19] Now, there is ongoing interest in developing systems or methods that can incorporate and use existing electronic data to enable active surveillance for ADEs,[20] and this surveillance for signal detection of ADEs is feasible.[21] Prescription sequence symmetry analysis (PSSA) is a signal detection method for ADEs utilizing administrative claims data[22] and is based on analyzing the sequences of medications; if one medication (marker drug) is more often initiated after another medication (index drug) than before, it may be an indication of an adverse effect of the index drug.[23] Validation studies have indicated that the PSSA has moderate sensitivity and high specificity, and has robust performance.[23] PSSA has become a tool to assist in global pharmacosurveillance of medicines, complementary to other methods, and a pharmacovigilance tool to identify unsuspected side effects.[23,24] The method has been increasingly used to investigate safety concerns of medications, including ace-inhibitor induced cough, inhaled corticosteroid induced oral candidiasis, nonsteroidal anti-inflammatory induced stroke, and isotretinoin and cardiovascular medicine induced depression.[25] To our knowledge, only one Chinese study reported the association between statins and liver injury using PSSA,[26] but no other study has evaluated ATO-associated hepatotoxicity based on the PSSA.

The health insurance data are an important source of information for medical research,[27] which usually contains each patient's unique encrypted identification number, age, sex, diagnosis, medical treatment administered, whether the individual was an inpatient or outpatient, type of insurance, medical expenses, medical institution identification number, and prescriptions. The data are a valuable resource for exploratory analyses of a variety of health services research questions.[27] Based on the PSSA, the health insurance database can also be used for the study of ADEs/ADRs. This study aimed to evaluate ATO-associated hepatotoxicity using the PSSA, based on a health insurance database of a Chinese population in Jiangsu Province, China.

Patients and methods

Data source

Data for this study were obtained from the health insurance database of Jiangsu Province in 2017. A subset of data was used in the present study, including patients who were prescribed ATO or hepatoprotective drugs as single or combination products in either the inpatient or the outpatient setting. The variables in the data set included drug prescriptions (generic name and brand name of drugs, and prescription time) and patients' information (identification number, gender, age). The present study was approved by the Ethics Committee of Nanjing Medical University, and the data set does not contain any information that can identify subjects, such as names or addresses.

Definition of index and marker drugs

The index drug is the drug thought to produce a given side effect, while the marker drug is the drug used to alleviate the given side effect.[28] In the present study, the index drug is ATO, regardless of its manufacturer or dosage. The marker drugs, namely, hepatoprotective drugs, which were the most commonly used drugs in China, were categorized into five therapeutic classes: anti-inflammatory, antioxidant, antidote, choleretic, cell membrane repair agents (Table 1). Such categorization applied regardless of the manufacturer or dosage. In China, the patients with

Table 1 Hepatoprotective drugs included in the atorvastatin analyses

Therapeutic class	Hepatoprotective drugs
Anti-inflammatory agents	Magnesium Isoglycyrrhizinate, Diammonium glycyrrhizinate
Antioxidant agents	Bicyclol, Bifendate
Antidote agents	Reduced glutathione sodium for injection
Choleretic agents	Ademetionine 1,4-Buta nedisulfonate, Ursodeoxycholic acid
Cell membrane repair agent	Polyene phosphatidylcholine

drug-induced liver injury (DILI) can be treated with hepatoprotective drugs.[29] The international criteria established by the Council for International Organizations of Medical Sciences (CIOMS) is used for judging the DILI based on three clinical types.[29,30] (1) hepatocellular injury, alanine aminotransferase (ALT) ≥3 upper limit of normal (ULN) and R (the ratio of the elevation of baseline ALT to baseline alkaline phosphatase (ALP)) ≥5; (2) cholestatic injury, ALP≥2 ULN and R≤2; (3) hepatocellular-cholestatic mixed injury, ALT≥3 ULN, ALP≥2 ULN and 2<R<5.

Run-in period and time periods

The run-in period, namely, how long you would have to wait before a patient fills his first prescription for a given drug, was determined based on the "waiting-time" distribution.[22,31] The time intervals, the periods between the initiation of index drugs and marker drugs, were set at different days (15, 30, 60, 90, 120, and 180 days) to conduct the sensitivity analysis according to the reference.[26]

Statistical analysis

The PSSA method, originally described by Hallas,[22] was applied in this study. In brief, PSSA proceeds in three steps. First, patients who filled incident prescriptions of both index and marker drugs during 2017 are identified. Second, patients are classified on the basis of the temporal order of the alternative sequences of prescription events. The "causal" group consists of patients who filled the index drug first and the marker drug second, whereas conversely the "noncausal" group consists of patients who filled the index drug second and the marker drug first. Finally, the estimate of risk is calculated by taking the ratio of the number of patients in the "causal" to the "noncausal" groups.[22,32] The three key indicators were calculated as follows:

(1) The crude sequence ratio (CSR) is the ratio of the number of patients in the "causal" group over the number of patients in the "noncausal" group, which is a measure of the degree of asymmetry between the two patient groups.

(2) The null-effect sequence ratio (NESR) determines the expected sequence ratio given no cause-effect relationship between the index drug and the marker drug. The NESR measures differential change in prescribing patterns during the study period, which could confound the CSR. NESR is defined as $a/(1-a)$[33] where a is given as

$$a = \frac{\sum_{m=1}^{u} ATO_m \sum_{n=m+1}^{m+d} HD_n}{\sum_{m=1}^{u} ATO_m \left(\sum_{n=m-d}^{m-1} HD_n + \sum_{n=m+1}^{m+d} HD_n\right)}$$

In the aforementioned formula, m or n is the consecutive days of the survey period (excluding the run-in period) and u is the last day of the survey period. HD is an abbreviation for hepatoprotective drug. HD_{index} is the number of patients being prescribed hepatoprotective drugs first on the index day, and ATO_{index} is the number of patients being prescribed ATO first on the index day. d is the time interval between ATO and the hepatoprotective drugs.

(3) The adjusted sequence ratio (ASR) was calculated for each time interval as the CSR divided by the NESR (ASR=CSR/NESR). 95% confidence intervals (95% CI) for the ASRs were calculated by using a method for exact confidence intervals in binomial distributions.[34]

Stratified analysis was conducted according to different genders and ages, and the difference between the two groups was analyzed by the χ^2 test. Findings were considered statistically significant at an alpha level of 0.05 if the 95% CI did not include the null (1.0). All calculations were performed using STATA (version 13.0, Stata Corp, College Station, Texas, USA).

Results

The study database contains records on 10,318 patients with 73,388 prescriptions of ATO or hepatoprotective drugs over the period from January 1, 2017, to December 31, 2017. Among these patients, 4,480 patients prescribed both ATO and hepatoprotective drugs in the same year were identified. Five hundred eighty-two patients were excluded from the analysis because of being prescribed both drugs on the same day. As shown in Figure 1, the "waiting-time" distribution curves showed a steeply descending limb, reaching a more or less stable plateau after 30 days. Therefore, the other 1,349 patients were excluded because the run-in period was less than 30 days. Of the remaining 2,549 patients, 1,518 filled the ATO prescription first and 1,031 filled the ATO prescription second (Figure 2). A slight asymmetry was observed in the distribution between prescription orders (Figure 3).

After setting the time interval between the initiation of index and marker drugs as 15, 30, 60, 90, 120, and 180 days, the ASRs were 1.492 (95% CI: 1.367–1.652),

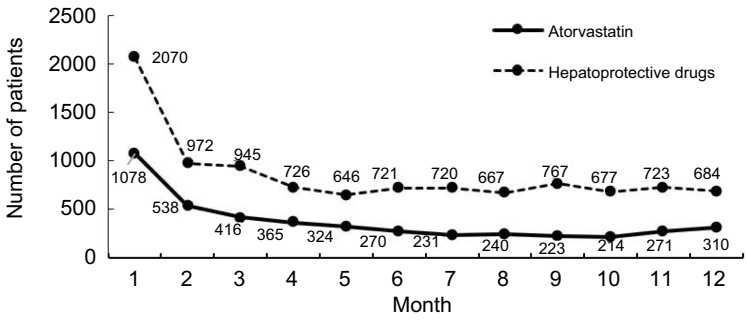

Figure 1 Waiting-time distributions for patients of atorvastatin and hepatoprotective drugs during the period January 2017 to December 2017.

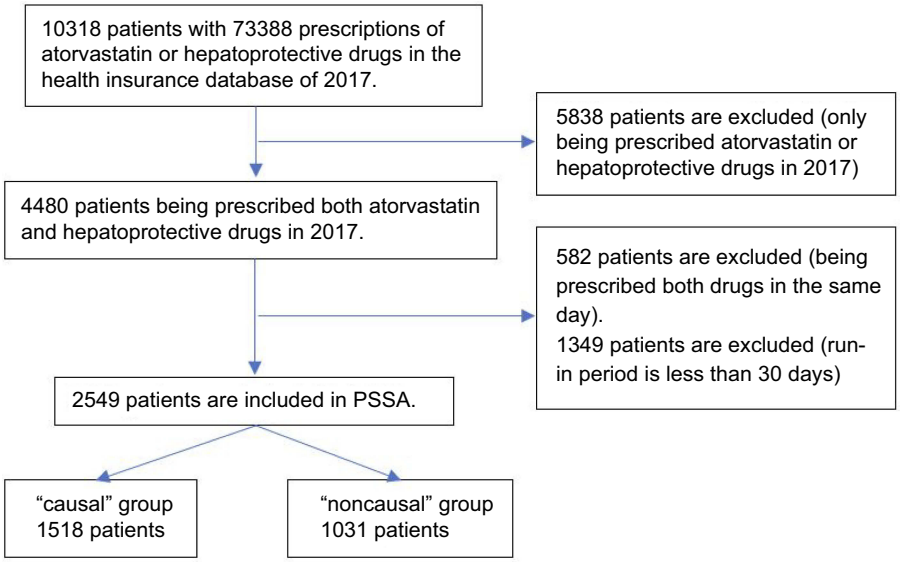

Figure 2 A flow chart of patients' inclusion and exclusion.

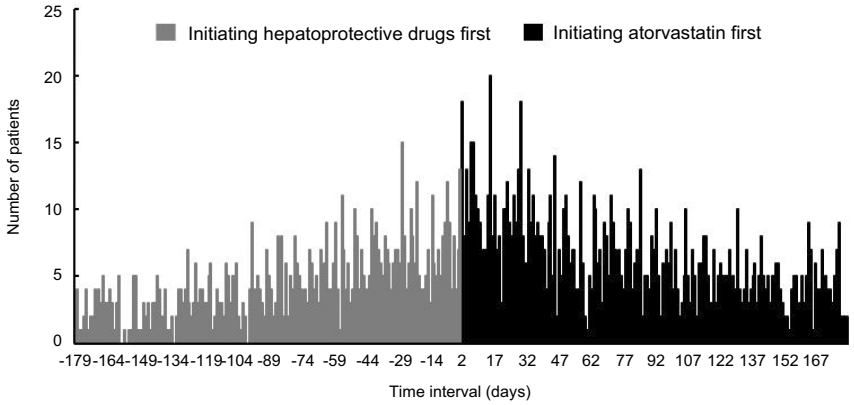

Figure 3 Frequency distribution of patients by days before or after atorvastatin initiation within 180 days.

1.399 (95% CI: 1.308–1.508), 1.280 (95% CI: 1.213–1.357), 1.292 (95% CI: 1.234–1.356), 1.278 (95% CI: 1.226–1.336), and 1.274 (95% CI: 1.229–1.323), respectively (Table 2). The ASRs showed a downward trend as the extension of the time interval, and the positive signal was stronger within 30 days' time interval.

An extended stratified analysis was conducted according to different genders and ages, and the results are shown

Table 2 Results from the atorvastatin analysis, by different characteristics

Characteristics	Study population (N)	"Causal" group (n)	"Noncausal" group (n)	CSR	NESR	ASR (95%CI)
Time interval (days)						
≤15	277	166	111	1.495	1.002	1.492 (1.367–1.652)
≤30	527	309	218	1.417	1.013	1.399 (1.308–1.508)
≤60	931	528	403	1.310	1.023	1.280 (1.213–1.357)
≤90	1276	731	545	1.341	1.038	1.292 (1.234–1.356)
≤120	1541	888	653	1.360	1.064	1.278 (1.226–1.336)
≤180	1972	1159	813	1.426	1.119	1.274 (1.229–1.323)
Gender*,†						
Male	477	276	201	1.373	1.040	1.320 (1.228–1.430)
Female	454	252	202	1.248	1.003	1.243 (1.150–1.354)
Age (years)*,‡						
<60	430	249	181	1.376	0.979	1.405 (1.303–1.529)
≥60	501	279	222	1.257	1.058	1.188 (1.104–1.289)

Notes: *Setting the time interval as ≤60 days. †Comparison between groups, χ^2=0.161, *P*=0.688. ‡Comparison between groups, χ^2=1.565, *P*=0.211.
Abbreviations: CSR, crude sequence ratio; NESR, null effect sequence ratio; ASR, adjusted sequence ratio; 95% CI, 95% confidence interval.

in Table 2. The ASRs were 1.320 (95% CI: 1.228–1.430) and 1.243 (95% CI: 1.150–1.354) in males and females, respectively; 1.405 (95% CI: 1.303–1.529) and 1.188 (95% CI: 1.104–1.289) in patients age <60 and ≥60 years, respectively. No significant difference was observed between different genders and ages (χ^2=0.161, *P*=0.688; χ^2=1.565, *P*=0.211, respectively).

Discussion

This study is the first to evaluate the association of ATO with the potential risk of hepatotoxicity using PSSA in a Chinese population. Based on the health insurance database and the PSSA, we confirmed the relationship between the index drug (ATO) and the marker drugs (hepatoprotective drugs) (The ASRs were more than 1 under different time intervals, and 95% CI did not include the null), which indicated that the possibility of ATO-induced hepatotoxicity in a Chinese population. There is a 1.3- to 1.5-fold increase in the risk of hepatotoxicity in the present study, especially within 30 days of initiating ATO first. To date, only one study has explored the relationship between statins and the risk of hepatotoxicity, which showed the potential association between statins and liver injury.[26] In that study, the ASR of statins was 1.471 (95% CI: 1.395–1.550), and the ASR of ATO was 1.419 (95% CI: 1.335–1.508),[26] similar to that of the present study. Additionally, the results of ADRs monitoring from different countries also suggested that ATO may cause hepatotoxicity. ADRs reports received by the Swedish Adverse Drug Reactions Advisory Committee in 1988–2010 showed that a statin-related DILI was reported in 1.2/100,000 users, and ATO was implicated in 30/73 (41%) of the cases.[17] Between April 1994 and August 2012, the Spanish Hepatotoxicity Registry indicated that statin-related DILI was not common in Spain, but ATO was the statin involved in the greatest number of incidents (16/47, 34%).[35] In prospective studies of patients with DILI, statins have been the cause in approximately 2–5% of patients, and ATO has been the most frequently implicated statin in all of the series of statin induced hepatotoxicity.[16] The present study also verified ATO-associated hepatotoxicity using PSSA, and this signal detection method may be a fast and effective one in drug safety evaluation and can also be implemented based on a health insurance database.

Although rare, ATO-induced hepatotoxicity has been well documented, and different hepatotoxicity mechanisms have been proposed.[18] Multiple studies suggested that

ATO-induced autoimmune hepatitis is responsible for most idiosyncratic drug reactions.[16,36,37] However, no significant association was observed for human leukocyte antigen-A, -B and -C alleles with ATO-induced hepatotoxicity in a Japanese population.[38] Evidence from cell and animal experiments suggest that it may also be related to other mechanisms. HMG-CoA reductase inhibitors can induce apoptosis by increasing intracellular reactive oxygen species generation.[39] ATO caused liver tissue dysfunction as well as hepatic cell death via oxidative stress-induced cell signaling pathways, including the signals from the mitochondria, caspases and calpain in a dose-dependent manner.[40] Thymoquinone, a prominent constituent of Nigella sativa, has antioxidant, anti-inflammatory and anti-apoptotic activity, and posttreatment thymoquinone can reverse high-dose ATO-induced hepatic oxidative injury in rats.[41] Additionally, inhibition of HMG-CoA reductase by statins reduces the production of mevalonate, a precursor of coenzyme Q10.[42] Even brief exposure to atorvastatin causes a marked decrease in blood coenzyme Q10 concentration.[43] Coenzyme Q10 is one of the most significant lipid antioxidants and its co-administration has been shown to improve particular atorvastatin side effects stemming from oxidative stress.[44,45] Therefore, oxidative stress induced by ATO or its metabolites, and the reduction of coenzyme Q10 may contribute to the development of ATO-induced hepatotoxicity. Furthermore, ATO and its metabolites are predominantly eliminated by ATP-binding cassette (ABC) transporters (ABCB1 and ABCG2) mediated transport from liver into bile.[46] A variation (rs2032582) in *ABCB1* was also significantly associated with ATO-induced hepatotoxicity (G allele versus T and A alleles, OR=2.59, 95% CI: 1.49–4.50, P=0.00068).[38] All these potential mechanisms, on the one hand, illustrate the complexity of the mechanism of ATO-induced hepatotoxicity, and on the other hand, indicate that ATO does cause liver injury in patients initiating ATO. Therefore, it is necessary to strengthen patient monitoring and timely detect cases of hepatotoxicity, especially within 30 days of initiating ATO.

In addition to ATO, other statins have been implicated in the liver injury as well.[18] However, only ATO and simvastatin have been associated with fatality from statin induced liver injury.[16] Therefore, if the patients cannot tolerate ATO, other statins could be used for lipid-lowering treatments, such as fluvastatin, lovastatin, pravastatin and rosuvastatin.[16] In addition, some natural lipid-lowering drugs are also safe, effective and well tolerated in Chinese patients, such as Chinese medicine Zhabitai,[47] Xuezhikang[48] and so on.

Limitations and strengths

Our study has several strengths. PSSA is a simple form of a self-controlled design that is able to analyze effects of drugs normally used for chronic conditions, and the effect of the measured and unmeasured confounders is automatically canceled out when the effect is stable over the study period.[33] Although this is a pilot study based on data for one year, we only included all first-time patients of ATO and hepatoprotective drugs to exclude the influence of nonfirst-time patients. The run-in period was determined by plotting the number of patients who were first-time users each month to find the stable plateau. Sensitivity analysis under different time intervals was used to detect the signal and find which time period the signal was stronger. Our study also has some limitations. First, using hepatoprotective drugs as a proxy for hepatotoxicity is not perfect. On the one hand, it is possible that some physicians would discontinue ATO treatment if they suspected that abnormal liver function in patients was related to ATO. On the other hand, in addition to the hepatoprotective drugs mentioned in this study, there are some other Chinese herbal medicines that may be used to treat hepatotoxicity but were not included as the marker drugs. Second, we did not investigate the dose-response relationship between ATO and hepatotoxicity in the study because only patients who had both the marker and index drugs were included in the analyses. Third, although generic ATO is as effective as the brand-name drug in lowering cholesterol levels,[49] we didn't distinguish whether ATO was a generic or brand name drug because of the limited sample size.

Conclusion

To the best of our knowledge, this is the first study conducted in a real-world setting to evaluate the relationship between ATO and hepatotoxicity using the PSSA in a Chinese population. We found a 1.3- to 1.5-fold increase in risk of hepatotoxicity following ATO, with the greater risk occurring within the first 30 days of treatment. Our findings may help guide patient education at the initiation of treatment with ATO for lowering cholesterol levels. PSSA is effectively applied as a safety signal detection tool for recently marketed medicines, and would be more widely used in the monitoring of ADEs/ADRs signals in future.

Acknowledgments

This study was funded by the National Natural Science Foundation of China (81373066) and Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

Author contributions

Haiping Zhang, Miaomiao Yang, Yinchu Cheng, and Shaowen Tang contributed to the study concept and design and take responsibility for the integrity of the data and the accuracy of the data analysis. Haiping Zhang, Jiani Wu, Zhuolin Zhang, Haisheng Qian, Yifan Wang and Miaomiao Yang obtained and conducted statistical analysis. Haiping Zhang drafted the report, which was edited by Shaowen Tang. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work. All authors have reviewed and approved the final version of manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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