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Postprint: Analysis of Clinical Features of Atorvastatin-Induced Liver Injury

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Abstract

Background Drug-induced liver injury is one of the most common adverse drug reactions. Atorvastatin, a widely used statin lipid-lowering drug in clinical practice, can readily cause liver injury. Currently, research data on the clinical characteristics of atorvastatin-induced liver injury remain limited. Objective To investigate the clinical characteristics of atorvastatin-induced liver injury and improve clinicians' understanding of this condition. Methods We selected patients hospitalized at the First Affiliated Hospital of Guangxi Medical University between January 2012 and August 2022, who received atorvastatin therapy, developed liver injury, and were assessed as having atorvastatin-induced liver injury using the Roussel Uclaf Causality Assessment Method, and analyzed their clinical characteristics. Results A total of 84 cases of atorvastatin-induced liver injury were diagnosed using the Roussel Uclaf Causality Assessment Method. The patients were predominantly male (72.6%), with a mean age of (60.2$±$11.5) years, and all had comorbidities (100.0%). Two cases developed moderate liver injury (2.4%), and the cure or improvement rate after treatment was 100.0%. According to disease course classification, all cases manifested as acute (100.0%). Based on target cell damage pattern classification, the mixed type was most common (60.7%), followed by cholestatic type (26.2%) and hepatocellular type (11.9%). Liver injury occurred within 3 months of atorvastatin administration in 78.6% of patients, predominantly within the first 1-2 weeks. In 80.0% of patients, liver injury occurred when the cumulative dose reached 80 defined daily doses (DDD). Conclusion Atorvastatin-induced liver injury occurs more frequently in male, middle-aged and elderly patients with comorbidities, is mostly mild with a favorable prognosis, and is predominantly classified as mixed or cholestatic type. The onset of liver injury mainly occurs within 3 months, and the occurrence of atorvastatin-induced liver injury exhibits certain dose-dependency.

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Full Text

Clinical Characteristics of Atorvastatin-Induced Liver Injury

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Abstract

Background: Drug-induced liver injury (DILI) is one of the most common adverse drug reactions. Atorvastatin is a widely used statin lipid-lowering drug in clinical practice that can cause liver injury, yet research data on the clinical characteristics of atorvastatin-induced liver injury remain limited.

Objective: To investigate the clinical characteristics of atorvastatin-induced liver injury and improve clinicians' understanding of this condition.

Methods: We selected hospitalized patients at the First Affiliated Hospital of Guangxi Medical University from January 2012 to August 2022 who were treated with atorvastatin, developed liver injury, and were assessed as having atorvastatin-induced liver injury using the Roussel Uclaf Causality Assessment Method (RUCAM), then analyzed their clinical characteristics.

Results: A total of 84 cases of atorvastatin-induced liver injury were diagnosed by RUCAM assessment. Patients were predominantly male (72.6%) with a mean age of (60.2$±$11.5) years, and all had comorbid underlying diseases (100.0%). Two cases (2.4%) reached moderate liver injury, with a cure or improvement rate of 100.0% after treatment. According to disease course classification, all cases presented as acute (100.0%). Based on target cell damage classification, the mixed type was most common (60.7%), followed by cholestatic type (26.2%) and hepatocellular type (11.9%). Liver injury occurred within 3 months of atorvastatin administration in 78.6% of patients, predominantly within the first 1-2 weeks. Eighty percent of patients developed liver injury when the cumulative dose reached 80 defined daily doses (DDD).

Conclusion: Atorvastatin-induced liver injury occurs mainly in male, middle-aged and elderly patients with underlying diseases, mostly presents as mild liver injury with favorable prognosis, and is predominantly classified as mixed or cholestatic type. Liver injury typically occurs within 3 months, and the development of atorvastatin-induced liver injury shows some dose-dependency.

Keywords: Atorvastatin; Drug-induced liver injuries; Signs and symptoms

Introduction

Drug-induced liver injury (DILI) is one of the most common adverse drug reactions, with numerous drug classes capable of causing it. The annual incidence of DILI in the Chinese population is 23.80 per 100,000, while in developed countries it ranges from 1 to 20 per 100,000. Given China's large population base, DILI represents a serious public health challenge. As disease patterns have shifted, the incidence of chronic cardiovascular and cerebrovascular diseases remains high, leading to increasingly widespread use of atorvastatin. As an inhibitor of the rate-limiting enzyme in cholesterol synthesis, atorvastatin is primarily metabolized by hepatic cytochrome P450 3A4 and exhibits lipophilic properties. Studies have shown that atorvastatin is one of the most commonly used statins associated with a relatively high incidence of liver injury, yet clinical data on the characteristics of atorvastatin-induced DILI remain scarce. To improve medication safety, this study analyzes the clinical characteristics of patients with atorvastatin-induced DILI diagnosed through RUCAM assessment, aiming to enhance clinicians' awareness and provide a reference basis for early detection, diagnosis, and treatment.

Methods

Study Subjects

We selected hospitalized patients at the First Affiliated Hospital of Guangxi Medical University from January 2012 to August 2022 who developed liver injury during atorvastatin treatment and were assessed as having atorvastatin-induced DILI using RUCAM. Inclusion criteria were: (1) no abnormal liver function before atorvastatin administration; (2) RUCAM score $\geq$ 3 points. Exclusion criteria were: (1) pre-existing abnormal liver function before atorvastatin administration; (2) liver injury caused by viral hepatitis, alcoholic hepatitis, autoimmune liver disease, metabolic-associated liver disease, tumors, toxins, pesticides, or other causes.

DILI Classification

(1) According to disease course: acute DILI (liver function returns to pre-illness levels within 6 months of onset) and chronic DILI (liver function remains abnormal after 6 months, or there is evidence of portal hypertension or chronic liver damage on imaging or histology). (2) According to the Council for International Organizations of Medical Sciences (CIOMS) criteria for target cell damage, we calculated the R-value as: R = (observed ALT ÷ ULN of ALT) / (observed ALP ÷ ULN of ALP). R $\geq$ 5

indicates hepatocellular type, R $\leq$ 2 indicates cholestatic type, and R = 2-5 indicates mixed type.

DILI Severity Grading

Severity was classified into grades 0-5 according to the 2017 Guidelines for the Diagnosis and Treatment of Drug-Induced Liver Injury, as shown in Table 1 .

Efficacy Evaluation Criteria

Based on reference [9]: (1) Cure: complete disappearance or significant improvement of symptoms and signs after treatment, with liver function indicators returning to normal range; (2) Improvement: reduction in symptoms and signs after treatment, with liver function indicators decreasing by >50% from pre-treatment levels; (3) No improvement: no improvement in symptoms and signs after treatment, with liver function indicators showing minimal improvement or progressive deterioration.

Defined Daily Dose (DDD)

The DDD is the most commonly used metric in drug utilization research, representing the average daily maintenance dose for adults for a drug's main therapeutic indication. According to the WHO ATC/DDD index (http://www.whocc.no/atc_{{{ddd}}_{{index}}}/), the DDD for atorvastatin is 20 mg.

Results

RUCAM Scale Scores

Among the 84 patients with RUCAM scores $\geq$ 3, 4 cases (4/84, 4.8%) had scores >8, 65 cases (65/84, 77.4%) scored 6-8, and 15 cases (15/84, 17.6%) scored 3-5, as shown in Table 2 .

Demographics and Comorbidities

The cohort was predominantly male (72.6%) with a male-to-female ratio of 2.65:1. Patient ages ranged from 34 to 89 years, with a mean age of (60.2$±$11.5) years. All 84 patients (100.0%) had comorbid underlying diseases, with cardiovascular diseases being most common (63/84, 75.0%), followed by metabolic diseases (61/84, 72.6%), cerebrovascular diseases (44/84, 52.4%), and 22 patients (22/84, 26.2%) had all three conditions, as detailed in Table 2 . The time to liver injury after atorvastatin administration ranged from 1 day to 5 years. Most patients developed liver injury within 3 months of atorvastatin use, predominantly within the first 2 weeks, as shown in Table 4 .

Classification by Disease Course

All 84 patients with atorvastatin-induced DILI showed improvement within 6 months, consistent with acute DILI (100.0%).

Classification by Target Cell Damage

Among the 84 patients, 51 (51/84, 60.7%) had the mixed type, 22 (22/84, 26.2%) had the cholestatic type, and 10 (10/84, 11.9%) presented with the hepatocellular type. Details of clinical classification are shown in Table 3 .

Time to DILI Onset

Eighty percent of patients developed DILI within 3 months of starting atorvastatin, predominantly in the first 1-2 weeks.

Relationship Between DILI and Drug Dose

Due to unclear dosage or administration timing in 5 patients, we analyzed the cumulative dose in 79 patients. The minimum dose at which atorvastatin DILI occurred was 1 DDD (20 mg), and the maximum was 1,196 DDDs (23,920 mg). Graphical analysis showed that 80% of patients developed liver injury when the cumulative dose reached 80 DDDs (1,600 mg), as shown in Table 5 .

Severity and Prognosis

Patients predominantly had mild liver injury (82/84, 97.6%), with only 2 cases (2/84, 2.4%) reaching moderate severity and no cases of severe injury. Seventeen patients (17/84) met discontinuation criteria (ALT/AST elevation $\geq 3\times$ ULN or progressive liver injury), while 67 did not. After active treatment, all 84 patients were cured or showed improvement.

Discussion

The clinical manifestations of DILI are nonspecific, lacking specific serological and imaging tests, and remains a diagnosis of exclusion, representing a challenge and focus of clinical research. Causality assessment is the primary method for confirming DILI. The RUCAM scale is currently recognized as the most comprehensive, relatively simple, reproducible, and widely used causality assessment method. All 84 patients in this study were evaluated using the RUCAM scale, meeting the diagnosis of atorvastatin-induced DILI, with 82.2% classified as highly probable or probable.

This study found that atorvastatin-induced DILI patients were predominantly male (72.62%), middle-aged and elderly (>60 years accounting for 47.6%), and mostly had underlying diseases, consistent with the findings of Chen et al. This may be related to hormonal effects on drug metabolism, age-related decline in organ function leading to slower drug metabolism and reduced tolerance to

drug toxicity, and the fact that middle-aged and elderly patients often have multiple comorbidities requiring polypharmacy, increasing the risk of DILI. The increased risk of atorvastatin DILI in middle-aged and elderly male patients warrants greater clinical attention and strengthened preventive monitoring.

Hyperlipidemia patients often have comorbidities requiring multiple medications, and drug interactions can affect the distribution and metabolism of atorvastatin. Atorvastatin is metabolized by hepatic cytochrome P450-3A4, and interactions with drugs sharing this metabolic pathway can increase DILI risk. This study found that among concomitant medications, major CYP450-3A4 substrates included clopidogrel, calcium channel blockers, sulfonylureas, and glinides. Patients with underlying diseases and these medications should receive enhanced DILI education to prevent disease progression.

Most patients had mild liver injury, with only 2 reaching moderate severity. Seventeen patients met discontinuation criteria (ALT/AST $\geq 3\times$ ULN or progressive injury), while 67 did not. All patients were cured or improved after treatment, indicating favorable prognosis. Wang et al. reported that timely drug discontinuation and comprehensive hepatoprotective and anti-inflammatory treatment achieved a cure/improvement rate of 92.31%. When DILI occurs, clinicians must weigh the risks of discontinuation against continued hepatic injury to select appropriate treatment. Although atorvastatin DILI mainly presents as elevated liver enzymes, severe cases have been reported, warranting vigilance.

The clinical classification of atorvastatin DILI correlates with severity and prognosis. All 84 patients showed acute disease course, related to mild severity and timely management. The mixed type was most common, followed by cholestatic and hepatocellular types, consistent with Andrade et al.

DILI typically occurs within 1-4 weeks of drug initiation or rechallenge. This study found 80.0% of patients developed DILI within 3 months, predominantly in weeks 1-2. Clinicians should be vigilant during the first 3 months, especially within 2 weeks, for early detection and treatment. Atorvastatin DILI shows dose-dependency. Studies show statins have a "rule of six"—doubling the dose only reduces LDL-C by an additional 6% without significant clinical benefit while increasing adverse effects and reducing compliance. In this study, 80% of patients developed injury at 80 DDDs (1,600 mg), suggesting that monitoring timing can be guided by cumulative dose to reduce disease and economic burden.

Conclusion

In summary, atorvastatin-induced DILI occurs mainly in male, middle-aged and elderly patients with underlying diseases, mostly presents as mild liver injury with favorable prognosis, and is predominantly classified as mixed or cholestatic type. Liver injury typically occurs within 3 months, and the development of atorvastatin DILI shows some dose-dependency.

Author Contributions

JIANG Linshuang was responsible for study conception and design, data collection and analysis, and manuscript writing. CHEN Maowei was responsible for results verification, manuscript revision, quality control and review, and overall supervision.

Conflict of Interest

The authors declare no conflict of interest.

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