

## Frequency of statin-induced liver injury: A secondary analysis of previous hospital-based study

Abdel-Monem Badawi Yousif<sup>1</sup>, Ebtihal Abdelmoneim Hassan<sup>2</sup>

From <sup>1</sup>Senior Pharmacist, Department of Pharmacy, <sup>2</sup>Consultant, Department of Accident and Emergency, Hamad General Hospital, Doha, Qatar

### ABSTRACT

**Background:** Although statins are considered safe, they do have side effects with a wide range of hepatic adverse effects. The present study aims to estimate the frequency of liver injury in patients treated with various statins and to describe their clinical characteristics and outcomes. **Materials and Methods:** We carried out a secondary *post hoc* analysis of collected data from our previous study entitled “Frequency of Rhabdomyolysis in Patients Treated with Statins in Hamad General Hospital, Qatar.” **Results:** We identified 10 cases (1.0%) of statin-induced liver injury during the study period. Their mean age was 62±10.09 years, with 6 (60%) males and 4 (40%) females. Of the 10 patients, six patients received rosuvastatin, two patients received atorvastatin, and other two cases received simvastatin. The mean duration between the initiation of statin and the development of liver injury (latency period) was 20.40±6.91 months. Five of our patients were asymptomatic, and liver injury was discovered incidentally during routine testing of the patients during routine follow-up, while four patients developed painless jaundice and one developed muscle pain attributed to rhabdomyolysis. Statins were stopped in all patients. Nine of them were managed on an outpatient basis, while one patient with rhabdomyolysis was admitted. In all patients, other statins were reintroduced after a mean time of 7.4±3 months without recurrence of liver injury. No mortality has been reported. **Conclusion:** Our study demonstrated that statin-induced liver injury is a rare clinical entity that occurs regardless of the dose and type of statin, with rosuvastatin being the most causative drug. Statin-induced liver injury was asymptomatic and was discovered incidentally in 50% of our cases during routine testing, underscoring the importance of routine follow-up of liver function tests in asymptomatic patients.

**Key words:** Atorvastatin, Rosuvastatin, Simvastatin, Statin-induced liver injury

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are among the most prescribed drugs worldwide, which have seen rapid growth in recent years given encouraging data from clinical trials on the utility of these agents in the primary and secondary prevention of cardiovascular disease. More than 143 million prescriptions are issued annually in the United States of America [1]. Although statins are considered safe, they do have side effects with a wide range of hepatic adverse effects. Asymptomatic and usually temporary elevation of transaminases is among the most common side effects, and it is rarely clinically significant and usually occurs in the early stages of therapy [2]. This phenomenon is called transaminitis as it is thought to be related to alteration of hepatocyte cellular membrane with enzyme leakage rather than direct liver injury [3]. In a systematic review conducted by Kashani *et al.*, the absolute risk of transaminase elevations was significantly higher with

statin therapy in comparison with placebo [4]. Nevertheless, significant elevations of these enzymes are rare and have been reported in 1–3% of cases [5–7].

Statins are among the most frequently prescribed drugs in Qatar, with more than 120,000 prescriptions issued each year. However, little is known about the side effects of statins, especially liver damage. The present study aims to estimate the frequency of liver injury in patients treated with various statins and to describe their clinical characteristics and outcomes in our local setting.

### MATERIALS AND METHODS

#### Study Design, Setting, and Population

We carried out a secondary *post hoc* analysis of collected data from our previous study entitled “Frequency of Rhabdomyolysis in Patients Treated with Statins in Hamad General Hospital, Qatar” [8] with a modified objective to estimate the frequency

#### Access this article online

Received - 25 January 2022  
Initial Review - 09 February 2022  
Accepted - 17 February 2022

DOI: 10.32677/yjm.v1i1.3286

#### Quick Response code



**Correspondence to:** Abdel-Monem Badawi Yousif, Department of Pharmacy, Hamad General Hospital, P. O. Box: 3050, Doha, Qatar. E-mail: mabdelmonem209@gmail.com

© 2022 Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC-ND 4.0).

of statin-associated liver injury in this cohort. The primary study was designed to assess the frequency of rhabdomyolysis in patients treated with different statins for the period between January 1, 2017 and December 31, 2017, and it was approved by the Medical Research Committee at Hamad Medical Corporation (# MRC-01-18-232).

### Definitions, Inclusion, and Exclusion Criteria

The liver injury was defined as follows [6]:

1. Raising alanine transaminase (ALT) or aspartate transaminase levels  $\geq 5$  upper level of normal (ULN)
2. Alkaline phosphatase  $\geq 2$  ULN
3. The combination of an increase in ALT  $>3$  ULN and total bilirubin  $>2$  ULN

Cases that met the criteria for liver injury, in addition to the chronology between statin drug use and the onset of hepatic dysfunction with subsequent rapid improvement on cessation of statins, were included in the study, while patients with other causes of liver injury were excluded from the study.

### Data Analysis

Data were reported as the mean  $\pm$  standard deviation (SD) with the range for quantitative variables, whereas qualitative variables were described as numbers and percentages.

## RESULTS

Among the 1000 patients recruited in the primary study, we identified only 10 cases (1.0%) with statin-induced liver injury during the study period. Their mean age was  $62 \pm 10.09$  years (range: 53–83 years), with 6 (60%) males and 4 (40%) females. Of the 10 patients with liver injury, six patients received rosuvastatin, two patients received atorvastatin, and other two cases received simvastatin. The mean duration between the initiation of statin and development of liver injury (latency period) was  $20.40 \pm 6.91$  months (range: 8–27 months). Five of our patients were asymptomatic and liver injury was discovered incidentally during routine testing of the patients during routine follow-up, while four patients developed painless jaundice and one developed muscle pain attributed to rhabdomyolysis. Statins were stopped in all patients. Nine of them were managed on an outpatient basis, while one patient with rhabdomyolysis was admitted and received intravenous fluid. In all patients, other statins were reintroduced after a mean time of  $7.4 \pm 3$  months (range: 2–12 months) without recurrence of liver injury. Table 1 presents the demographic and clinical characteristics of patients who developed statin-induced liver injury. No mortality has been reported.

## DISCUSSION

There is a paucity of studies on the frequency of statin-induced liver injury, with most data drawn from case reports or small

retrospective or prospective studies. To the best of our knowledge, our study is the first in Qatar to describe the incidence of statin-induced liver injury. Initially, statins were thought to have a high risk of causing drug-induced liver injury. When first approved for use in the United States, baseline liver function tests (LFTs) were recommended before starting the statin and routine monthly monitoring thereafter [1]. Since then, the significance and utility of routinely monitoring LFTs following the initiation of statin therapy have been a subject of debate until NICE guidelines recommended baseline LFTs testing before initiating statin therapy, then within 3 months, and at 12 months, followed by testing only if the patient develops any symptoms related to the side effects of statins [9]. On the other hand, the American College of Cardiovascular Administrators/American Hospital Association guidelines recommend measuring baseline LFTs, followed by testing only when clinically indicated as prior efficacy trials have demonstrated no benefit in preventing clinically significant liver injury [1,10]. However, our findings, showing that 50% of our cases were discovered incidentally during routine testing, highlight the challenging question of monitoring for liver injury in patients receiving statin therapy. Thus, we recommend the routine follow-up testing of LFTs in asymptomatic patients at least in the initial few months when the risk of hepatotoxicity is highest.

The occurrence of statin-induced liver injury has been reported by some studies with different frequencies, based on the criteria utilized for diagnosis. The incidence of true liver injury caused by statin is noticed to be around 1% [11], which is consistent with our finding. A characteristic element of statin-induced liver injury is that it may present with several phenotypes capable of resembling other liver diseases. Moreover, since specific markers for hepatotoxicity are still not available, it is difficult to prove causality without rechallenge, which is not without risk, leading some researchers to recommend against rechallenge if significant liver injury occurs [12]. However, in the study by Bjornsson *et al.* [13], statin-induced liver damage could only be confirmed in three out of 73 cases with rechallenge, and the diagnosis depended mostly on the exclusion of other causes as well as a consistent chronology between drug intake and the onset of liver dysfunction. Similarly, in our study, rechallenge was not applied, and the diagnosis was based on the exclusion of other causes as well as a consistent timeline between drug ingestion and the onset of liver impairment and return of transaminases to baseline.

*Idiosyncratic* liver injury due to statins has been reported in 1.9–5.5% of patients in a prospective series of drug-induced liver injury [14]. Rather, we found that liver damage occurred regardless of statin dosage in all patients. The interval between drug initiation and the development of liver injury (latency period) varies between 5 weeks and 6 months [1,3,5,6,10-13]. However, prolonged latency periods for a year or more have been reported [1,15]. In our series, the mean latency period was  $20.40 \pm 6.91$  months (range: 8–27 months), and 80% of the cases exhibited prolonged latency periods for a year or more. Atorvastatin is the most common cause of clinically significant liver injury among statins with a reported incidence of 1/17000

**Table 1: Demographic and clinical characteristics of the patients with statin-induced liver injury**

Variables	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age	81	54	57	62	60	60	83	58	57	53
Sex	M	M	M	F	M	M	F	F	F	M
Nationality	Indian	Filipino	Austrian	Qatari	Indian	Indian	Qatari	Qatari	Qatari	Indian
BMI	33.8	28	36.6	37.1	26	29	40	29	30	26
Type of statin	Rosuva	Rosuva	Simva	Atorva	Atorva	Rosuva	Simva	Rosuva	Rosuva	Atorva
Duration (month)	12-24	>24	<12	>24	<12	12-24	>24	>24	>24	>24
Dose	10	10	10	40	40	20	20	20	20	20
Co- Morbidity										
CAD	Yes	No	No	No	Yes	Yes	No	No	No	No
COPD	No	Yes	No	No	No	No	Yes	No	No	No
CHF	No	No	No	No	No	No	Yes	No	No	No
Chronic liver disease	No	No	No	No	No	Yes	No	No	No	Yes
Diabetes mellitus	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hypertension	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No
CKD	Yes	No	No	No	No	No	Yes	No	No	No
Concomitant drugs										
Aspirin	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
ACEI/ARBs	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No
B-Blocker	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No
CCBs	No	No	No	No	Yes	No	No	Yes	Yes	No
Fenofibrate	No	No	No	No	No	No	Yes	No	No	No
Gemifibrate	No	No	No	No	No	No	No	No	No	No
Diuretics	No	No	No	No	Yes	No	Yes	No	No	No
ALT	179	146	105	142	138	406	93	135	99	137
AST	227	71	92	98	90	253	219	110	86	88
ALP	469	96	247	156	99	103	496	432	423	112
Bilirubin (µmol/l)	24	52	19	37	50	22	25	24	26	33
CK	96	80	85	57	93	123	3213	88	50	88
Management										
Statin discontinuation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Statin re-initiation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Re-initiated statin	Atorva	Prava	Rosuva	Rosuva	Rosuva	Atorva	Atorva	Atorva	Prava	Rosuva

Atorva: Atorvastatin, Simva: Simvastatin, Rosuva: Rosuvastatin M: Male, F: Female, AST: Aspartate transferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, BMI: Body mass index, ACEI: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin receptor blockers, CCBs: Calcium channel blockers, CK: Creatine kinase

users. On the contrary, our study demonstrated that rosuvastatin was the drug most implicated in liver injury.

The mechanism of statin-induced liver damage remains unclear and various mechanisms of hepatotoxicity have been proposed including mitochondrial dysfunction [16], immune-mediated [17], and the inhibition of the respiratory chain [18].

There are limited data on the risk of cross-toxicity between different statins in cases of statin-induced liver injury, and some authors discourage restarting statin after an episode of liver toxicity unless clinically necessary and no other suitable alternative is available. However, Liu *et al.* [19] reported two cases of atorvastatin-induced liver injury who were switched to pravastatin following the return of transaminases to baseline. Similarly, all patients in this series were switched to different statins following the return of transaminases to baseline without recurrence of liver injury (Table 1).

Patients with statin-induced liver injury generally have a good prognosis, with few reported fatalities associated with atorvastatin and simvastatin [14,15]. In our series, the outcomes were favorable for all types of statins and no mortality has been reported. Several limitations to the present study should be acknowledged. These limitations included the retrospective design, the small sample size (attributed to the low incidence of statin-induced liver injury) which did not allow us to perform advanced analysis to determine risk factors for statin-induced liver injury, and finally the implementation at a single center, making it difficult to generalize the study results.

## CONCLUSION

Our study demonstrated that statin-induced liver injury is a rare clinical entity that occurs regardless of the dose and type of statin,

with rosuvastatin being the most causative drug. Statin-induced liver injury was asymptomatic and was discovered incidentally in 50% of our cases during routine testing, underscoring the importance of routine follow-up of LFTs in asymptomatic patients. Statin withdrawal is the best therapeutic option, once liver injury is identified or suspected with switching to different statins following the return of transaminases to baseline.

## REFERENCES

- Russo MW, Hoofnagle JH, Gu J, *et al.* Spectrum of statin hepatotoxicity: Experience of the drug-induced liver injury network. *Hepatology* 2014;60:679-86.
- Clarke AT, Mills PR. Atorvastatin associated liver disease. *Dig Liver Dis* 2006;38:772-7.
- Jose J. Statins and its hepatic effects: Newer data, implications, and changing recommendations. *J Pharm Bioallied Sci* 2016;8:23-8.
- Chalasan N. Statins and hepatotoxicity: Focus on patients with fatty liver. *Hepatology* 2005;41:690-5.
- Kashani A, Phillips CO, Foody JM, *et al.* Risks associated with statin therapy: A systematic overview of randomized clinical trials. *Circulation* 2006;114:2788-97.
- Chitturi S, George J. Hepatotoxicity of commonly used drugs: Nonsteroidal anti-inflammatory drugs, antihypertensives, antidiabetic agents, anticonvulsants, lipid-lowering agents, psychotropic drugs. *Semin Liver Dis* 2002;22:169-83.
- Aithal GP, Watkins PB, Andrade RJ, *et al.* Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther* 2011;55:683-91.
- Perdices EV, Medina-Cáliz I, Hernando S, *et al.* Hepatotoxicity associated with statin use: Analysis of the cases included in the Spanish hepatotoxicity registry. *Rev Esp Enferm Dig* 2014;106:246-54.
- Yousif AB, Hassan EA, Ahmed MU, *et al.* Frequency of rhabdomyolysis in patients treated with statins in hamad general hospital, Qatar. *Libyan J Med Sci* 2021;5:75-8.
- National Institute for Health and Care Excellence. Cardiovascular Disease: Risk Assessment and Reduction, Including Lipid Modification; 2016. Available from: <https://www.nice.org.uk/guidance/cg181> [Last accessed on 2022 Jan 01].
- Stone NJ, Robinson JG, Lichtenstein AH, *et al.* 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. A report of the American college of cardiology/American heart association task force on practice guidelines. *Circulation* 2014;129:1-45.
- Chang CY, Schiano TD. Review article: Drug hepatotoxicity. *Aliment Pharmacol Ther* 2007;25:1135-51.
- Cohen DE, Anania FA, Chalasan N, *et al.* An assessment of statin safety by hepatologists. *Am J Cardiol* 2006;97:77-81.
- Björnsson E, Jacobsen EI, Kalaitzakis E. Hepatotoxicity associated with statins: Reports of idiosyncratic liver injury post-marketing. *J Hepatol* 2012;56:374-80.
- Björnsson ES. Hepatotoxicity of statins and other lipid-lowering agents. *Liver Int* 2017;37:173-8.
- Tolosa L, Carmona A, Castell JV, *et al.* High-content screening of drug-induced mitochondrial impairment in hepatic cells: Effects of statins. *Arch Toxicol* 2015;89:1847-60.
- Pelli N, Setti M, Ceppa P, *et al.* Autoimmune hepatitis revealed by atorvastatin. *Eur J Gastroenterol Hepatol* 2003;15:921-4.
- Halegoua-De Marzio VJ. Hepatotoxicity of cardiovascular and antidiabetic drugs. In: Kaplowitz N, DeLeve L, editor. *Drug-Induced Liver Disease*. 3<sup>rd</sup> ed. United States: Academic Press; 2013. p. 519-40.
- Liu Y, Cheng Z, Ding L, *et al.* Atorvastatin-induced acute elevation of hepatic enzymes and the absence of cross-toxicity of pravastatin. *Int J Clin Pharmacol Ther* 2010;48:798-802.

*Funding: None; Conflicts of Interest: None Stated.*

**How to cite this article:** Yousif AB, Hassan EA. Frequency of statin-induced liver injury: A secondary analysis of previous hospital-based study. *Yemen J Med*. 2022;1(1):27-30.