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Evaluating the derangement of LFTs concerning statin use and probable liver injury among non-cardiac patients, in the light of R ratio.

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Abstract

Background: To evaluate the derangement of Liver Function Tests (LFTs) concerning statin use and probable liver injury among non-cardiac patients in light of the R ratio.

Methodology: This retrospective observational cohort study was conducted at Sindh Government Hospital Liaquatabad (SGHL) in Karachi, including 142 non-cardiac patients. Both male and female patients, aged ≥ 18 years, continuously using statin irrespective of dose or duration, were included in the study. While non-alcoholic fatty liver disease (NAFLD) patients, those with alcoholic liver diseases, chronic or acute hepatitis, chronic renal failure, disorders of the thyroid or parathyroid glands, cardiovascular, endocrine and any other disease that might alter or elevate liver enzymes, recreational drug users, smokers, users of tobacco products and those patients using herbal medications were excluded from the study sample. The data regarding patients' characteristics, including demographics and clinical characteristics (LFTs result and treatment), were obtained from the hospital records and noted using a structured questionnaire. The R ratio for suspected drug-induced liver injury was calculated following the American College of Gastroenterology (ACG) guidelines. The statistical analysis was performed on SPSS version 22.0

Results: The enrolled patients predominantly used rosuvastatin 20 mg/day 124(87.3%), and the mean duration of statin use after the first prescription was 18.28 ± 14.33 months. The LFT levels were mildly elevated concerning statin use, and this borderline elevation did not require further investigation, nor was there any evidence of clinical liver injury. The mean R ratio was 1.81 ± 0.56; most cases presented a cholestatic picture 86(60.6%) complementing the liver safety profile of statins in patients without cardiac diseases.

Conclusion: In conclusion, statins use caused only borderline clinically and statistically insignificant elevations in the LFTs over time among non-cardiac patients.

Keywords

Drug-Induced Liver Injury, Statins, Liver Function Tests.

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Introduction

Despite the relative success of the project initiated by the Council for International Organizations of Medical Sciences for defining significant diagnostic tools and criteria for casualty assessment of Drug-Induced Liver Injury, the global incidence rate remains on the rise, and the diagnosis remains challenging[1-3]. Adverse drug reactions are a significant factor in liver damage, which may necessitate stopping the offending medication, staying in the hospital, or even undergoing liver transplantation[4]. The liver is a target for medication-induced harm because it concentrates and metabolizes the majority of medications. Acetaminophen (paracetamol) is the hepatotoxic drug that is most frequently researched. However, a wide variety of different pharmaceutical substances, can cause liver damage. Numerous conventional medical treatments and herbal remedies can also be hepatotoxic.

Male gender and older age are linked to cholestatic forms of DILI while females are more likely to contract hepatitis and progresses to acute liver failure[5]. The toxicity from drugs is more common among individual with liver pathologies. For instance, hepatitis B or C may worsen the inflammatory side effects of antituberculosis drugs[6]. It is also well known that drinking alcohol frequently makes drugs more toxic[7]. Additionally, due to increased cytochrome p450 system activation, which results in the production of the toxic metabolite acetaldehyde, acetaminophen is particularly toxic in heavy alcohol drinkers. Additionally, it is understood that non-alcoholic fatty liver disease can raise a person's vulnerability to DILI[8]. As a result, special care must be taken when treating liver disease patients[9]. However, the use of potentially hepatotoxic medications is not prohibited in the presence of pre-existing liver disease. For instance, statins are frequently prescribed to NAFLD patients. Polymorphisms of the cytochrome p450 enzymes have been linked to genetic factors predisposing patients to DILI, as it either slows the toxic drugs metabolism or speeds up bioreactive drug metabolites production[10,11].

It is typical to establish a temporal correlation between drug exposure and the onset of liver disease symptoms and signs in order to make the drug-induced liver injury diagnosis. It's crucial to rule out any autoimmune, infectious, or other liver conditions. A correct diagnosis is made on the basis of a comprehensive medical history and a high clinical suspicion. An experienced clinician will actively look into the latency period i.e., time interval between drug administration and the onset of pathology. Drugs with dose-dependent toxicity typically cause clinical symptoms to appear within hours to days, whereas immune-mediated reactions may take weeks to appear after the drug has been administered. The improvement following drug withdrawal is a crucial aspect that aids in confirming drug-induced liver damage. Higher hepatic enzymes and bilirubin levels are linked to the diagnosis of drug-induced liver injury. These abnormalities can have a hepatocellular, cholestatic, or mixed pattern. The hepatocellular pattern, which reflects the destruction of hepatocytes and may be linked to a worse prognosis, is characterized by elevated levels of the enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Acetaminophen toxicity can cause liver enzyme levels to rise above 20,000 IU/L. Elevated alkaline phosphatase levels are the most common laboratory sign of cholestatic DILI. There are no clear-cut histopathological signs of drug-induced liver damage. Eosinophilia may be a sign of a better prognosis, whereas the degree of hepatocyte necrosis may indicate a worse outcome[12].

The clinical spectrum of drug-induced liver injury can range from being completely asymptomatic and benign to causing acute liver failure[13]. Unlike many other medical conditions, the definitive diagnosis cannot be established in this case, as there is no single biochemical indicator or test. Its diagnosis is further heightened by the fact that virtually drug-induced liver injury can mimic all forms of acute and chronic liver disease. Roussel Uclaf Causality Assessment Method (RUCAM) is used frequently to assess liver and drug-causing injuries[14]. Although its reliability and validity have not been determined, it has led to the

development of new approaches to drug-induced liver injury. Most recently, an easy-to-use and feasible tool for the assessment of drug-induced liver injury was introduced by the American College of Gastroenterology (ACG), i.e., the R ratio[15]. It requires only LFTs for calculating the score that can be classified as the hepatocellular, cholestatic or mixed picture. Although the R ratio alone cannot identify the patterns of liver injury alone, but in combination with Hy's law, it significantly rules out liver injury. In addition, the drug patterns for the R ratio over the years have proven to be fairly specific. Therefore, this tool can also be effective in singling out the culprit medication where multiple drugs are involved[16].

The role of statins in improving all case mortality for cardiovascular diseases is all too well known. Nevertheless, more and more adults have been prescribed statins for non-cardiac diseases as well. These relatively young non-cardiac patients usually have dyslipidemia, which is the primary target of statins. Targeting dyslipidemia singly has opened up new frontiers for statin use. Hence, its consumption has rapidly boosted in the healthcare sector, and so have the side effects. Although liver toxicity is rare but mild derangement in the alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level is frequent. The relationship between statins and Liver Function Tests (LFTs) is complicated. As among liver disease patients, statins improve the levels of ALT and AST.

Therefore, this study aimed to analyze the effect of statins on deranged liver enzymes and probable liver injury among non-cardiac patients in light of the R ratio in order to acquire a better understanding of the drug-induced liver injury.

Methodology

In this observational cohort study, conducted at Sindh Government Hospital Liaquatabad (SGHL) in Karachi from March to November 2019, patient data was obtained retrospectively from hospital medical records. A total of 142 non-cardiac patients were included in the study using consecutive non-probability sampling techniques. Eligible patients of either gender, aged 18 years or older, who were continuously using statin irrespective of dose or duration, were enrolled.

To ensure the study's validity, certain exclusion criteria were applied. Patients with non-alcoholic fatty liver disease (identified on the basis of clinical indicators such as abnormal liver function tests (elevated ALT and AST), presence of hepatic steatosis on imaging studies (ultrasound, CT, MRI), and absence of significant alcohol consumption or other known causes of liver disease), alcoholic liver diseases, chronic or acute hepatitis, cardiovascular diseases (such as ischemic heart disease, acute coronary syndrome, arrhythmia, coronary artery disease, myocardial infarction, congestive heart failure), chronic renal failure, disorders of the thyroid or parathyroid glands, endocrine abnormalities, and any other conditions that might alter or elevate liver enzymes were excluded. Recreational drug users, smokers, users of tobacco products, and patients using herbal medications were also excluded from the study.

Patient data, including demographic and clinical characteristics, liver function test (LFT) results, and treatment details, was obtained and recorded using a structured questionnaire. Efforts were made to ensure data accuracy and reliability. Bias was controlled by adhering to ethical guidelines and maintaining patient confidentiality throughout the study.

The R ratio, an indicator of suspected drug-induced liver injury, was calculated following the guidelines issued by the American College of Gastroenterology (ACG). The R ratio was calculated using the upper limit of normal (ULN) for alanine transaminase (ALT) and alkaline phosphatase (ALP) obtained from local assays. The ULN values for ALT and ALP were 41 IU/L and 116 IU/L, respectively. The formula used for calculating the R ratio was:

$$\textbf{R ratio} = \frac{\textbf{ALT} \div \textbf{ULN ALT}}{\textbf{ALP} \div \textbf{ULN ALP}}$$

The R ratio was categorized as follows: a value < 2 indicated cholestatic damage, 2-5 indicated a mixed picture, and a value > 5 demonstrated

hepatocellular damage. Values < 0.3 and > 15 were considered erroneous and not recorded.

Data analysis was performed using SPSS version 22.0. Descriptive statistics, such as mean, median, and range, were calculated for continuous variables, including age, LFTs (ALT, AST, and ALP), duration of statin use, and the R ratio. Categorical variables, such as gender, type of statins used, co-morbid conditions, and R ratio categories, were presented using frequency and percentage. For inferential analysis, chi-square tests and independent samples t-tests were applied, with a significance level of $p < 0.05$ considered statistically significant.

Results

Of the total 142 patients enrolled, the majority were females 90(63.4%), as shown in table 1. The mean age of the patients was 53.69 ± 16.99 years. Dyslipidemia was the most commonly observed co-morbid condition, present in 97% of the patients, followed by hypertension 11(7.7%) and diabetes mellitus 6(4.2%). The mean duration of statins use was 18.28 ± 14.33 months, and 124(87.3%) patients were already consuming Rosuvastatin (20 mg/day) at the time of inclusion in the study, followed by Atorvastatin 18(12.7%).

Table 1: Patient 's baseline characteristics (n=142).

Variables		N(%)
Age (years); Mean±SD		53.69±16.99
Gender	Female	90(63.4)
	Male	52(36.6)
Co-morbid conditions	Dyslipidemia	138(97.1)
	Hypertension	11(7.7)
	Diabetes Mellitus	6(4.2)
Types of statin used	Rosuvastatin (20 mg/day)	124(87.3)
	Atorvastatin (20 mg/day)	18(12.7)
Duration of statin use (months); Mean±SD		18.28±14.33

*Values are given as Mean±SD or n(%)

Table 2 shows the alterations in the mean alanine transaminase (ALT), aspartate transaminase (AST), and Alkaline phosphatase (ALP). Mostly mild or borderline elevations were observed in the liver enzymes with respect to statin use. The mean ALT, AST, and ALP were 47.04 ± 14.51 IU/L, 41.37 ± 11.92 IU/L, and 85.43 ± 14.76 IU/L, respectively.

Table 2: Alterations in the liver function tests of the patients with respect to statin use.

Variables	Normal range (IU/L)[18]	Mean ± SD (IU/L)
Alanine transaminase	15-41	47.04±14.51
Aspartate transferase	8-46	41.37±11.92
Alkaline phosphatase	35-116	85.43±14.76

Table 3 shows that the mean R ratio in the enrolled patients was 1.81 ± 0.56; most patients had a cholestatic pattern of drug-induced liver injury 86(60.6%), while 56(39.4%) demonstrated a mixed pattern. Comparisons of the cholestatic and mixed pattern of DILI showed that the cases with the mixed pattern were younger (52.82 ± 11.46 years) as compared to those with cholestatic damage (54.25 ± 8.24 years), but there was no significant difference between the two patterns in terms of age (p=0.388). Similarly, no significant difference was found

between cholestatic and mixed pattern cases by the duration of statins used (17.72 ± 15.43 months vs. 19.14 ± 12.39 months; p=0.564). A significantly higher proportion of patients on both Rosuvastatin and Atorvastatin had the cholestatic type of liver injury compared to the mixed pattern. Otherwise, no significant differences were revealed between the two patterns (p=0.571).

Table 3: The R ratio values and categories in the study population (n=142).

Variables		N(%)
R ratio value (mean±SD)		1.81±0.56
R ratio categories	Cholestatic	86(60.6)
	Mixed picture	56(39.4)

*R ratio < 2 Cholestatic Damage; 2-5 Mixed Picture.

Discussion

Although the safety of statins is well established among patients with cardiovascular and fatty liver disease, even in the presence of deranged LFTs, previous data has evinced improvement of liver enzymes with long-term use of statins[17,18]. Our results are akin to such reports, but we did not record alterations in LFTs over time. The median value for ALT and AST, having ruled out multiple liver diseases, was 42 and 45, respectively. This borderline elevation did not require further investigation, nor was there any evidence of clinical liver injury. Therefore, even without using any objective scale, it was easy to mark out statin safety with respect to LFTs or drug-induced liver injury in patients without cardiac diseases. Minor derangements in LFTs should not deter physicians from prescribing statins unless there is a strong suspicion of underlying liver disease other than drug-induced liver injury.

Historically statins have demonstrated both cholestatic and hepatocellular patterns of drug-induced liver injury, with cholestatic representing far better outcomes. The cholestatic pattern resolves faster on stopping the offsetting therapeutic agent and is associated with milder and reversible liver injury[19]. However, the chances of progression to chronic liver disease (not cirrhosis) are higher with cholestatic drug-induced liver injury[19,20]. None of the patients had the R ratio > 5 (hepatocellular), which is further testament to the liver safety profile of statins in patients without cardiac diseases. Nearly all patients demonstrated cholestatic R ratio values.

The mean R ratio in the enrolled patients was 1.81 ± 0.56; most patients had a cholestatic pattern of drug-induced liver injury (60.6%), while 39.4% demonstrated a mixed pattern. Unlike other studies, none of the patients in the present study developed a hepatocellular drug-induced liver injury; the comparison of cholestatic and mixed DILI showed that the cases with the mixed pattern were younger as compared to those with cholestatic damage, with no significant difference (p=0.388). In comparison, Russo et al.,[21] observed 12 hepatocellular and 9 cholestatic categories based on the initial ratio (R ratio) out of 21. They further added that among the hepatocellular and cholestatic cases, those having hepatocellular patterns were younger, but there was no significant difference between the two patterns in terms of age, type of statin used, gender, BMI, etc., except for the level of ALT and R ratio (p<0.01).

However, the inclusion of patients with Vitamin D deficiency could have also altered our results as reduced vitamin D levels lead to elevation of ALP[22], resulting in lower (cholestatic/mixed) R ratio values. Certainly, this is one variable that brings into question the validity of the R ratio. There are many causes of raised ALP, and very few of them are due to liver disease; the most frequent among these is vitamin D deficiency[23]. This means any disease process that affects ALP levels can alter R ratio values. These inaccuracies and alterations

significantly reduce the sensitivity and specificity of the R ratio, in our opinion, and perhaps new research and insight into the equation (for the R ratio) are required.

Literature also confirms the association between prolonged latency and statin-induced liver damage. Given that most drug-induced liver injury cases are apparent within six months, Russo et al. found that 22.7% of patients enrolled in their study were taking medication for over a year or so before experiencing the injury; this extended time to onset is unusual[21]. Furthermore, rather than acute hepatocellular or cholestatic hepatitis, medications that are typically associated with a long latency present with a chronic hepatitis-like syndrome. Most statins, including Atorvastatin, simvastatin, fluvastatin, and Rosuvastatin, are frequently associated with prolonged latency and presented with both hepatocellular and cholestatic patterns of liver injury. In the present study, no significant difference was found between cholestatic, and mixed patterns of DILI related to the duration of statins used (p=0.564). A significantly higher proportion of patients on both Rosuvastatin and Atorvastatin had a cholestatic type of liver injury compared to the mixed pattern. Otherwise, no significant differences were revealed between the two patterns (p=0.571).

Apparently, histopathology is superior and remains the gold diagnosing and staging standards for liver diseases such as autoimmune hepatitis, Wilson's disease, overlap syndromes, and drug-induced liver injury[20]. But due to its invasive nature and scarcity of skilled technical experts, it is not performed in every suspected case. It is reserved for cases where a diagnosis cannot be made despite extensive testing.

Limitations

Even though the present study portended favorable outcomes, but several factors limited the study scope. Most notably, we were unable to follow the derangement of LFTs over time using statins. Furthermore, the effect of any other therapeutic agent, nutritional, caloric, and lifestyle effects on LFTs weren't considered.

Conclusion

It is concluded from the study results that statins can be safely prescribed to non-cardiac patients for the treatment of dyslipidemia. Statins rarely cause clinically significant liver enzyme elevations or damage; the R ratio values in the present cohort using statins displayed a cholestatic picture, which portends favorable outcomes.

Conflicts of Interest

The authors have no conflicts of interest.

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