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Case Report

Rare Clinically Significant Idiosyncratic Drug Induced Liver Injury Caused by Low Dose Atorvastatin: Time for a New Approach to Surveillance and Risk Identification

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Abstract

Background: Atorvastatin is a member of the class of cholesterol lowering drugs called statins, which works by inhibiting HMG-CoA reductase, an enzyme involved in cholesterol synthesis in the liver. Statins are used to reduce the risk of cardiovascular events in individuals who have risk factors or a history of cardiovascular disease. While atorvastatin is generally well-tolerated, like all statins, it can have some adverse effects, including Drug induced liver injury (DILI) which is rare and often dose related. However, there is scarcity of reports on symptomatic DILI occurring in patients on low dose statin and normal baseline liver function test. This case adds to the growing body of literature on the potential idiosyncratic, non-dose related adverse effects associated with atorvastatin therapy. Case report: A 69-year-old woman with history of Hypertension, Hyperlipidemia, Prediabetes, Non-Alcoholic Fatty Liver Disease (NAFLD) presented to her Primary care Physician (PCP) for regular follow up. Her Lipid panel in the last 1 year has been suboptimal with her Atherosclerotic Cardiovascular disease (ASCVD) risk score between 12.0-15.1% despite lifestyle modification. Patient was started on 10 mg of Atorvastatin daily after documenting normal baseline liver function test. Fifty-six days later, patient presented to the PCP's office with symptoms of fatigue, nausea and, right upper abdominal pain for 3 days. She had right upper abdominal tenderness and was mildly icteric. Based on her PCPs suspicion for DILI, she was advised to discontinue atorvastatin and transferred to the emergency room for further evaluation. In the Emergency room her vitals remained stable. Liver Ultrasound showed normal sized liver with features of hepatic steatosis. Laboratory analysis showed elevated alanine aminotransferase (ALT) greater than 16 times Upper limit of normal (ULN), aspartate aminotransferase (AST) greater than 9 times ULN, while alkaline phosphatase (ALP) elevation was less than 2 times ULN suggesting hepatocellular pattern. She was seen by a hepatologist 1 week later and other etiologies of acute hepatitis were ruled out. Over the course of 4 weeks, her symptoms completely resolved and liver function tests continued to improve. Forty-six days after Atorvastatin was discontinued, her aminotransaminases returned to normal levels. Conclusion: Although DILI is usually dose dependent, this case emphasizes the need for constant monitoring of liver function test of patients on low dose statins including patients with normal baseline liver function test. Personalized medical approach involving validated predictive score for DILI may become increasingly important in tailoring statin therapy to minimize the risk of adverse effects.

Keywords

Drug Induced Liver Injury, Hepatotoxicity, Idiosyncrasy, Statins

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1. Introduction

Statins are an extensively prescribed class of drugs to reduce cholesterol. Their primary mode of action is through inhibition of Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthesis pathway [1]. Atorvastatin was approved for use in the United States in 1996, with more than 50 million prescribed yearly and a cohort study showing increasing trend in statin use among adults 40 years and older from 17.9% in 2002-2003 to 27.8% in 2012-2013 [2, 3]. Atorvastatin like other statins reduces Low density lipoprotein (LDL) cholesterol levels which is a major risk factor for complications of atherosclerosis, including myocardial infarction, stroke and peripheral vascular disease which can be life-threatening [2]. Statins also exert cardiovascular pleiotropic effects that are independent of LDL-cholesterol lowering such as stabilizing atherosclerotic plaques, reducing platelet reactivity, reducing cardiac hypertrophy and fibrosis, and increasing endothelial nitric oxide synthase expression and activity in endovascular cells [4]. Common adverse effects of statin therapy include statin associated muscle symptoms, headache, joint aches, abdominal pain, neurocognitive effects, nausea and new onset type 2 diabetes mellitus that occur with all of the currently available statins. Rare but potentially severe adverse effects of statins include DILI and muscle toxicity causing myopathy, rhabdomyolysis, and immune-mediated necrotizing myopathy [1, 2].

The U.S. Preventive Services Task Force (USPSTF) recommends the use of moderate intensity statins for primary prevention of cardiovascular-related events and mortality in adults 40 to 75 years of age without known cardiovascular disease who have Diabetes Mellitus with LDL-C greater than 70 mg/dl, those with one or more cardiovascular disease risk factors (dyslipidemia, hypertension, or smoking) with an estimated 10-year cardiovascular disease risk of greater than 10% to less than 20% and, selectively for patients with risk of 7.5% to less than 10% [5]. The American Heart Association/American College of Cardiology (AHA/ACC) guideline consigns subclinical atherosclerosis to primary prevention requiring moderate-intensity statin therapy [6]. High-intensity statins are reserved for those having multiple risk factors (10-year risk for ASCVD ≥20%), LDL-cholesterol 190mg/dl or greater and secondary prevention for high-risk group (stable ASCVD) and very high-risk patients (multiple major ASCVD or 1 major ASCVD plus other high-risk conditions). LDL-cholesterol goal for patients on high intensity statin is less than 55 to 70mg/dl and greater than 50% reduction from baseline while a reasonable target for primary prevention through the use of moderate-intensity statin therapy is to maintain LDL-C within the range of 70-99 mg/dl [6, 7].

Statin-induced liver injury is generally considered a dose-dependent adverse effect, with a greater probability of occurrence at higher doses of statins. Most cases of statin-induced liver injury are mild and transient, while severe hepatotoxicity is infrequent occurring in about 0.001% of patients [1, 8]. Clinically apparent DILI occurring in patients on low-dose statins with normal baseline liver function tests is an extremely rare occurrence with few documented cases in literature [1, 8]. Most guidelines recommend obtaining baseline liver function studies prior to statin initiation for future comparison or identification of individuals with pre-existing dysfunction who may be at risk of drug-related injury. Current guidelines also emphasize close monitoring of patients with abnormal baseline liver test or decompensated liver disease [6, 7]. Currently, it is impossible to predict hepatotoxicity, particularly in patients on low-dose statins with normal baseline liver tests, due to its rare occurrence, making this case reportable [8].

2. Case Report

We present the case of 69-year-old African American woman with history of Hypertension, Hyperlipidemia, Prediabetes, Non-Alcoholic Fatty Liver Disease (NAFLD) with allergies to pork/porcine containing products, aspirin and penicillins presenting to her Primary Care Physician (PCP) for regular follow up. Her vitals during the visit were Blood pressure (BP) of 158/82 mmHg sitting (BP log range at home in the past 2 weeks was 140-162/89-98mmHg), Heart rate of 62, oxygen saturation was 98% on room air. Her Body mass index (BMI) was 26kg/m2. The rest of her examination was unremarkable. She was started on antihypertensive medications 2 years prior but she had not been adherent in the last 6 months. She had no history of cigarette smoking or Alcohol use disorder. Lipid panel in the last 1 year was suboptimal with her Atherosclerotic Cardiovascular disease (ASCVD) risk score between 12.0-15.1%. Initiation of statin therapy was discussed with her but she opted for lifestyle intervention including dietary restrictions and exercise. She was started on amlodipine 2.5mg to control her Blood pressure.

Lipid panel obtained 3 months later revealed total cholesterol of 202mg/dl (normal <200mg/dl) low density lipoprotein (LDL) of 140mg/dl (normal 0-130mg/dl), high density lipoprotein (HDL) of 41mg/dl (normal 40-60mg/dl) and triglycerides (TG) of 104mg/dl (normal <150mg/dl). Her blood pressure had improved to 138/80mmHg. Her baseline liver panel were normal as follows; albumin 4.3g/dl (normal 3.5-5g/dl), total bilirubin 0.4mg/dl (normal <1.2mg/dl), conjugated bilirubin 0.2mg/dl (normal <0.5mg/dl), alkaline phosphatase (ALP) 70U/L (normal <130U/L), aspartate aminotransferase (AST) 20U/L (normal <40U/L) and alanine aminotransferase (ALT) 19U/L (normal <19U/l). Baseline creatine kinase (CK) and kidney functions were within normal limits, but her glycated hemoglobin measured at 5.7%, indicating prediabetes. Her calculated ASCVD risk score based on her current clinical and lab parameters was 12.1%. Based on her cardiovascular risk, she was started on atorvastatin 10 mg daily. The benefits and risks

of atorvastatin therapy were discussed with patient.

Two months after commencing low dose atorvastatin, patient presented to the PCP, s office with symptoms of fatigue, nausea, right upper quadrant pain for 3 days prior to presentation. Vitals were unremarkable. She has right upper abdominal tenderness on examination and was mildly icteric. Pertinent negatives were absence of sore throat, normal oropharynx, no rash, no splenomegaly or lymphadenopathy. Her only routine medications were Amlodipine 2.5mg daily, Atorvastatin 10mg daily, calcium and vitamin D supplements. She denies intake of Acetaminophen, use new medications, Alcohol intake, herbal supplements or recent travels. Based on her symptoms and examination findings, there was a high suspicion for acute hepatitis viral versus drug (statin) induced liver injury). Patient was advised to stop atorvastatin and referred from the PCP, s office to the emergency department for further evaluation.

In the Emergency room, she was conscious and alert in time, place and person, her vitals were BP of 133/82mmHg, HR of 69 bpm, RR of 19/min and Temp 97.9F (36.6C). SARS-COV 2 PCR swab was negative. Her liver Ultrasound showed a normal sized liver with patchy increased echogenicity (Figure 1) and vascular blurring (Figure 2) representing parenchymal disease such as hepatic steatosis, and simple cyst in the left lobe of the liver measuring 1cm x 0.7cmx 0.7cm. Her gall bladder was contracted with negative sonographic Murphy sign (Figure 3). There was no intrahepatic biliary dilatation and her common bile duct measured 6mm. Her liver ultrasound results resembled those from an abdominal scan conducted two years earlier for an unrelated issue. Laboratory analysis in the Emergency room labs showed elevated ALT greater than 16 times upper limit of normal (ULN), AST greater than 9 times ULN, while ALP was elevation was less than 2 times ULN in keeping with a hepatocellular pattern of liver injury (Figure 4). She has also had mild conjugated hyperbilirubinemia (Figure 5). Hepatitis A, B, C, D and E serologies were unremarkable. Additional tests, including a complete blood count, international normalized ratio (INR) test, enteric fever screening, dengue testing, human immunodeficiency virus (HIV) serology, acetaminophen level, and serum lipase and amylase assessments, all yielded negative results.

She was discharged from the emergency department to be seen by a hepatologist 1 week later. During that visit, a series of tests were conducted to rule out other causes of acute hepatotoxicity and cystic liver disease, but the results were mostly unremarkable except for an elevated ferritin level (Table 1). Within a span of four weeks, her symptoms completely resolved, and her liver function tests improved during her recovery, eliminating the necessity for a liver biopsy. At the onset of DILI, ALT elevation was more marked than AST elevation. ALT reached its highest point at 487 U/L approximately 64 days after the initial dose of atorvastatin, while AST elevation peaked at 250 U/L around 57 days after the 1st dose of atorvastatin. About 14 weeks following the 1st dose of Atorvastatin and around 46 days after discontinuing the medication, her aminotransaminase levels returned to within normal limits making Atorvastatin highly probable as the cause of the patient's liver injury (Updated 2016 Roussel Uclaf Causality Assessment Method (RUCAM) points 9) (Figure 1). Four months after the onset of DILI, she had a follow-up appointment with her PCP, who advised her to abstain from alcohol use, limit tylenol intake, and to avoid use of herbal supplements without prescription. The patient remained committed to a healthy lifestyle and expressed her desire to avoid statins in the future. Nine months after the onset of DILI, her liver function tests remained normal, her lipid panel showed ongoing improvement due to strict dietary restrictions, and her ferritin levels had returned to normal. Her latest lipid panel revealed total cholesterol of 167mg/dl (<200mg/dl), LDL of 94mg/dl (0-130mg/dl), HDL of 42mg/dl (40-60mg/dl) and TG 112mg/dl (<150mg/dl). Her BP was controlled on amlodipine (persistently <130/80mmHg) putting her calculated ASCVD risk score at 9.6%.

Table 1. *Laboratory work up.*

Tests (normal values)	Results
Nuclear antibody screen with reflex IFA titer	Negative
Immunoglobulin panel	Within normal limits
Mitochondrial antibody qualitative	Negative
Anti smooth muscle antibodies	Negative
Anti liver-kidney microsome type 1antibodies	Negative
Anti-nuclear antibody	Negative
Anti ds-DNA	Negative
Viral hepatitis A, B, C and E Serologies	Negative
CMV (anti-CMV-IgM, anti-CMV-IgG)	Negative
EBV (anti-EBV-IgM, anti-EBV-IgG)	Negative
HSV (anti-HSV-IgM, anti-HSV-IgG)	Negative
VZV (anti-VZV-IgM, anti-VZV-IgG)	Negative
Echinococcus IGG	Negative
Entamoeba Histolytica IGG	Negative
C reactive protein (<0.8mg/dl)	<0.2mg/dl
Ferritin (10-150 ng/ml)	634ng/ml
Amylase (<100U/L)	99U/L
Lipase (<60U/L)	31U/L
Creatinine Kinase (<200U/L)	116 U/L
Gastrointestinal infectious panel	Negative
Stool for ova and parasite	Negative

CMV: Cytomegalovirus, EBV: Ebstein-Barr Virus, HSV: Herpes Simplex Virus, VZV: Varicella Zoster Virus

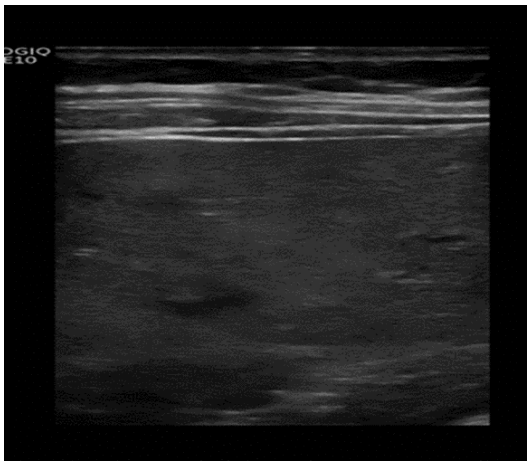

Figure 1. *Liver Ultrasound showing Incresed Echogenecity of the Liver.*

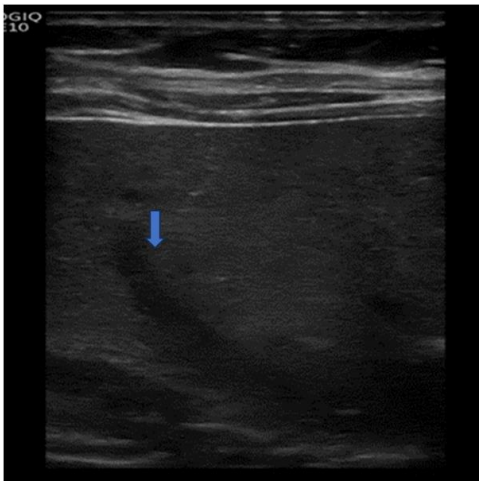

Figure 2. *Liver ultrasound showing Vascular blurring (Blue arrow).*

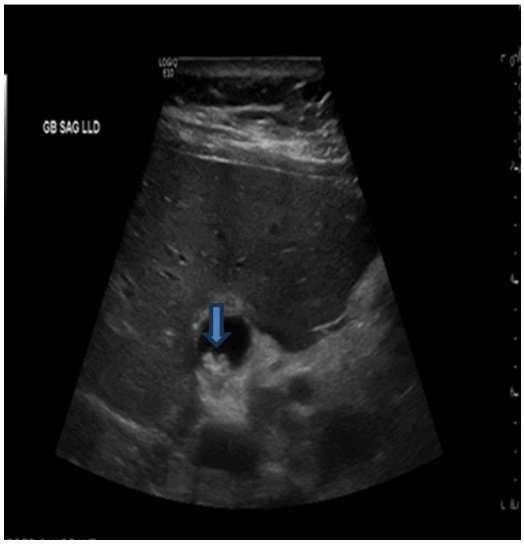

Figure 3. *Liver Ultrasound showing contracted Gall bladder with a calculus measuring 1.0x0.7x0.7cm (Blue arrow). There was absence of peri cholecystic fluid or localized tenderness while scanning over the Gall bladder.*

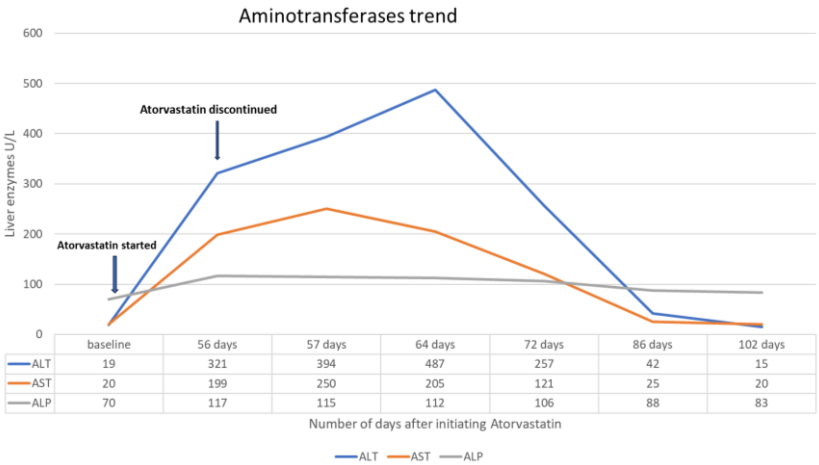

Figure 4. *Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and Alkaline Phosphatase (ALP) trend after initiation and discontinuation od atorvastatin.*

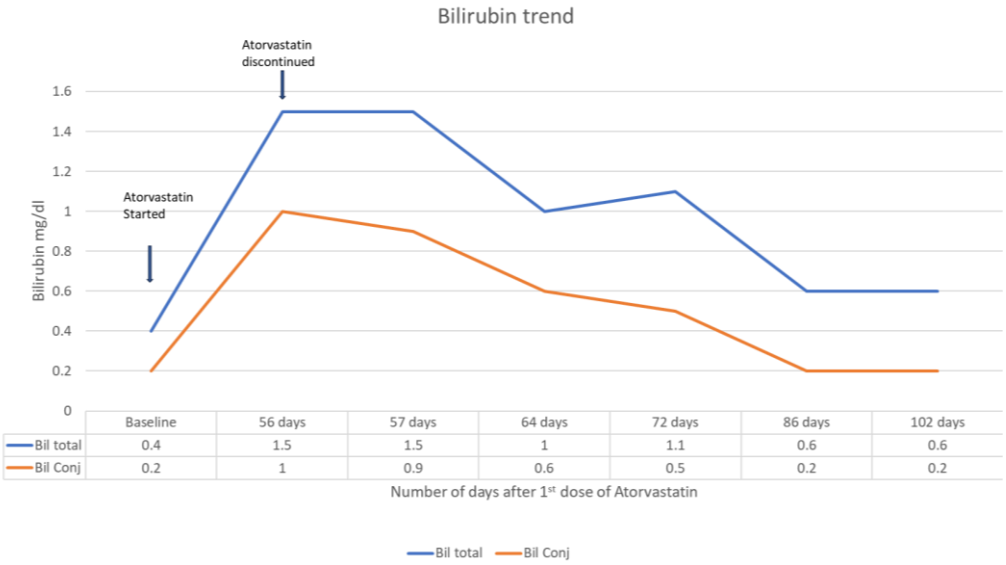

Figure 5. *Total and conjugated bilirubin trend after initiation and discontinuation of atorvastatin.*

3. Discussion

Drug induced Liver Injury (DILI) is a relatively rare and potentially serious adverse reaction to drugs or xenobiotics with symptoms mimicking acute and chronic liver diseases [9, 10]. DILI can be categorized as either direct (dose-dependent, intrinsic, and predictable) or idiosyncratic (largely dose-independent, idiosyncratic, affecting only susceptible individuals and unpredictable) [11, 12]. Idiosyncratic DILI is uncommon, occurring in only 1 in 1000 to 1 in a million exposed individuals [11]. However, the true incidence of DILI can be difficult to approximate, and the actual incidence may be greatly higher than that reported [13]. Acetaminophen is the most common cause of DILI causing acute liver failure in the United States while antibiotics especially amoxicillin-clavulanate and antiepileptics account for 60% world-wide [14]. Initial clinical trials of statins, while somewhat underpowered, detected a rise in aminotransferases in up to 2% of patients, with a rare occurrence of clinically apparent liver injury [1]. Among all statins, atorvastatin and simvastatin have been linked to over 50 case reports of liver injury, with idiosyncratic DILI attributed to statins reported in 1.9% to 5.5% of patients in prospective studies on drug-induced liver injury [15].

Although certain drugs have a distinct phenotype such as isoniazid, usually causing a hepatocellular pattern or chlorpromazine which presents as a cholestatic liver damage, many drugs including statins can lead to both hepatocellular and cholestatic injury [16]. Clinically apparent hepatic injury from atorvastatin is rare, occurring in ~1:3000 to 1:5000 treated patients [2]. The latency to onset of injury is also highly variable in literature ranging from 1 month to several years with most cases arising within 6 months [2]. The typical manifestation of DILI resulting from atorvastatin is cholestatic hepatitis, usually of mild to moderate intensity and with a self-limiting course. However, there have been reports of prolonged cholestasis with associated bile duct damage as well [2, 17, 18]. Atorvastatin hepatotoxicity can also cause a distinctly hepatocellular pattern of DILI with marked elevations in serum aminotransferase levels and minimal to no increase in alkaline phosphatase levels, which was the case in this patient [2]. The mechanism of Idiosyncratic DILI can be categorized as hypersensitivity (immunologic) or Metabolic. Hypersensitivity-type reactions are distinguished by fever, rash, granulomas, and eosinophilia in the peripheral blood or tissue biopsy sample, accounting for 23% to 37% of all idiosyncratic DILIs according to reports while the remaining cases are thought to be metabolic due to lack of features of hypersensitivity [19]. The mechanism of Atorvastatin induced liver injury is largely unknown. Autoimmune-like atorvastatin-induced liver injury with positive anti-nuclear antibodies and Anti-smooth muscle antibody has been found in some cases of DILI with hepatocellular pattern [2, 20]. Other proposed mechanisms of liver injury include oxidative stress form, toxic drug metabolites, apoptosis, haptenization and a failure to adapt [21].

There are recognized risk factors for atorvastatin induced DILI that should be considered prior to initiating treatment and during monitoring for potential hepatic adverse events. Liver injury caused by statins is typically regarded as an adverse effect that depends on the dosage, with a greater likelihood of occurring at higher statin doses [22]. Another risk factor for liver injury caused by atorvastatin is drug-drug interaction. As atorvastatin is metabolized by CYP4503A4, strong inhibitors of CYP 3A4 such as clarithromycin, HIV protease inhibitors, itraconazole, verapamil, clopidogrel and grapefruit juice can increase atorvastatin levels. In such cases, it is advisable to limit the dose to 20 mg daily or less according to reports [2, 23]. Pre-existing liver conditions, such

as non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, hepatitis, or cirrhosis, can increase the susceptibility to statin-induced liver injury [24]. These conditions may impair the liver's ability to metabolize and excrete statins effectively. On the contrary, other studies have shown that the risk of developing statin-induced DILI is not related to the presence of pre-existing liver abnormalities especially NAFLD [11]. Some studies even suggest that stain therapy improved liver test abnormalities and histology in patients with NAFLD [12, 18, 25]. Demographic factors, such as age, race, and gender, can also influence DILI risk, with older individuals, African Americans, and women being at a higher risk of statin-induced liver side effects [12, 24, 26].

Certain statins may have a slightly higher risk of causing liver injury than others. For example, atorvastatin and simvastatin have been associated with a slightly higher risk compared to other statins like pravastatin and rosuvastatin [1, 18]. Lipophilic statins and those extensively metabolized by hepatic mechanisms may increase risk of DILI [1]. This could explain why hydrophilic statins with dual hepatic and renal clearance such as Pravastatin and rosuvastatin are implicated to a lesser degree [1]. The most challenging aspect of DILI is the idiosyncratic response to drug exposure in individual patients, characterized by unpredictability, dose independency, low incidence, variable latency period and lack of experimental reproducibility [24]. Abnormal host immunity may be connected to most cases of idiosyncratic DILI [11].

Diagnosis DILI could be challenging requiring appropriate clinical context, timing of events and exclusion of differential diagnosis therefore high index of suspicion is essential [24]. Diagnostic scales like the Roussel Uclaf Causality Assessment Method (RUCAM) are valuable tools for assessing the causality of DILI. Clinically significant DILI criteria include aminotransferases greater than 5 times the ULN, and/or ALP greater than 2 times the ULN; or bilirubin greater than 2 times the ULN or greater than 2.5 mg/dl along with elevated serum AST, ALT, or ALP level; or INR greater than1.5 with elevated serum AST, ALT, or ALP [11, 27]. The RUCAM system identify likely causation by assigning points for clinical, biochemical, serologic and radiologic features of liver injury which gives an overall assessment score. The final score is interpreted as follows: A score of 0 or less indicates that the drug is ruled out as a cause, a score of 1 to 2 suggests it is unlikely, a score of 3 to 5 indicates it is possible, a score of 6 to 8 implies it is probable, and a score greater than 8 signifies it is highly probable [28]. Currently causality scales require improvement and refinement to enhance accuracy, reduce subjectivity, and incorporation of patient-specific factors and latest scientific evidence [21, 29]. Although not required for diagnosis and not always performed in DILI cases, liver biopsy may provide clues to the underlying DILI mechanisms, providing prognostic information, and guiding therapy [19]. The American College of Gastroenterology recommend liver biopsy if Autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated or, if liver biochemistry abnormalities persist beyond 180 days, with clinical features of liver injury [12].

Mild ALT elevations could be seen with Statin use and usually do not require intervention. However, if ALT levels rise above 10-fold normal, or persistently above 5-fold elevated or are associated with symptoms of liver injury, atorvastatin should be discontinued [2]. Atorvastatin induced clinically apparent DILI is usually self-limited and recovery is complete within few weeks to 4 months. Those with autoimmune component may require long term immunosuppressive therapy, suggesting that atorvastatin may trigger autoimmune hepatitis [2]. For cholestatic DILI, symptomatic treatments such as bile acid sequestrants or antihistamines for pruritis can be used with some efficacy [30]. Recurrence of DILI with rechallenge has been reported with atorvastatin and should be avoided [2]. Switching therapy to another statin after atorvastatin induced injury has been attempted with good outcomes [2]. It has been observed that atorvastatin and simvastatin appear to be the most implicated statins in hepatotoxicity, while fluvastatin, pravastatin, and rosuvastatin to a lesser extent [1]. There is also a documented case of autoimmune DILI with atorvastatin in which rechallenge with pravastatin did not lead to hepatotoxicity [20]. It might be prudent to initiate these less commonly implicated statins in patient with predisposing factors to hepatotoxicity when statin therapy is indicated or for rechallenge in patients with atorvastatin induced DILI. However, come authors caution rechallenge with another statin, underscored by a documented case of low dose rosuvastatin leading to rapid recurrence of DILI in a patient with prior simvastatin hepatotoxicity [31]. Rare acute liver failure from atorvastatin has also been reported in literature [2, 32]. While a few patients have experienced mortality or required liver transplantation due to statin-induced DILI, the vast majority of individuals with liver injury have recovered upon discontinuation of therapy [15].

The impact of harmful statin side effects is felt by both medical practitioners and individuals under their care. Despite a lack of evidence that statins commonly cause liver diseases, many health care providers are reluctant to start statins in patients with an out-of-range liver function test due to concerns about significant hepatotoxicity [20, 33, 34]. In addition, a review article noted that long term adherence to statin therapy even in the setting of secondary prevention is poor with some studies showing about 50% discontinuation rate after 6 months [35]. These non-adherence statistics are alarming despite the risk-to-benefit ratio of statin therapy and their effectiveness in reducing various cardiovascular events [35]. Hence, it is of utmost importance to rectify the unfavorable perception regarding statin-related adverse effects through the establishment of a novel framework for preemptive monitoring and risk assessment, aimed at averting DILI. Current guidelines recommend monitoring liver function during statin therapy based on individual patient risk and benefit assessment but may not explicitly emphasize frequent monitoring in patients on low-dose statins at risk of idiosyn-

cratic DILI [36]. It's crucial to review existing guidelines to personalize liver function monitoring during statin therapy by taking into account patient risk factors, medical history, concurrent medications, and the latest evidence, including biomarkers, pharmacogenetics, and predictive scores.

To prevent clinically significant DILI-related liver injury, early detection of the signal event is essential. A number of promising predictive, diagnostic and prognostic genetic biomarkers may aid our understanding, prevention and management of DILI [37]. MicroRNAs have gained attention as potential biomarkers for DILI due to their role in regulating gene expression and their stability in various body fluids [38]. Altered expression of specific microRNAs has been associated with various diseases, including DILI [38]. According to genome-wide association studies (GWAS), missense variant (rs2476601) in PTPN22, appears to be a risk factor for all - cause DILI across multiple racial and ethnic groups [39]. Other proposed biomarkers for prediction and early diagnosis of DILI includes markers of immune activation such as Cytokeratin-18, Sorbitol dehydrogenase, caspase-cleaved CytoKeratin-18, Hyperacetylated High Mobility Group Box protein-1 and Macrophage colony-stimulating factor receptor-1 [11, 24]. By integrating these biomarkers with clinical assessments, physicians can make informed decisions about patient care, including modifying medication regimens and guiding liver function monitoring protocols. However, established diagnostic serum marker for DILI is far from being validated.

As our understanding of the genetic basis of drug-induced liver injury continues to evolve, personalized medicine approaches that take into account an individual's genetic profile (pharmacogenetics) may become increasingly important in tailoring statin therapy to minimize the risk of adverse effects. GWAS findings have provided valuable insights into susceptibility genes and genetic variations, including transporter genes like OATPs and ABC genes, as well as genetic variations in CYP3A4 [27]. The cytochrome P450 (CYP) enzyme system, particularly CYP3A4, is involved in the metabolism of many drugs including statins. Genetic variations in CYP3A4 and other related genes can impact the rate at which statins are metabolized in the liver and also predispose to drug-drug interaction. This could explain why statins metabolized through non-CYP450 pathways, like pravastatin, or those with limited CYP2C9/8/19 metabolism, such as rosuvastatin, and fluvastatin (metabolized by CYP2C9) have a lower association with hepatotoxicity in comparison to statins metabolized by CYP3A4 (e.g., atorvastatin, lovastatin, and simvastatin) [1]. The US Drug-Induced Liver Injury Network (DILIN) prospective study is highlighting potential utility of human leukocyte antigens as DILI risk factors including new data on racial differences [40]. The index patient had a history of hypersensitivity to amoxicillin. In literature, HLA-DRB1 *1501-DRB5, *0101-DQB1 *0602 haplotype has been associated with increased susceptibility to amoxicillin hypersensitivity while the presence of HLA-B*57:01 and HLA-B*58:01 significantly elevates the risk of hypersensitivity reactions to abacavir and allopurinol respectively [26, 41, 42]. These observations underscore the need for more exhaustive studies on the genetic associations of drug hepatotoxicity.

According to a mouse model study, mitochondrial oxidative stress and susceptibility to membrane permeability transition may underlie statin hepatotoxicity [42, 43]. In the study, dietary supplementation with the antioxidants CoQ10 or creatine could reverse or prevent hepatotoxicity from statins [43]. Prospective collection of well-vetted DILI cases in established registries is a valuable approach in advancing our understanding of DILI and improving patient safety. By consistently collecting data on DILI cases, researchers can identify and validate variables such as patient demographics, medication details, laboratory results, comorbid conditions such as thyroid disease, underlying chronic liver disease and other risk factors that are most strongly associated with severe DILI outcomes [27, 44, 45]. This information may be helpful in creating predictive scores to assess the risk of DILI in individual patients [21, 29]. Validated predictive scores based on these data enables healthcare providers to make more informed decisions regarding medication choices, dosages, and monitoring protocols for patients at risk of DILI. Data from prospective registries can also support research into DILI mechanisms and causes, as well as ongoing post-marketing drug safety monitoring [21]. If certain medications consistently show a high risk of severe DILI in the collected data, regulatory agencies can take appropriate actions, such as updating labeling and issuing warnings.

4. Conclusion

It is important to note that statin-induced liver injury is relatively uncommon, and the majority of individuals who take statins do not experience significant liver problems. Additionally, the risk of liver injury must be weighed against the known cardiovascular benefits of statin therapy, which can be substantial for many patients at risk of heart disease. While DILI is commonly associated with higher doses of statins, it can still occur although rarely at lower doses. While many guidelines do recommend periodic monitoring of liver function during high dose statin therapy or presence of baseline abnormal liver function test, they might not explicitly emphasize the need for frequent monitoring in patients on low-dose statins with normal baseline liver function.

Given the potential risks associated with DILI, it is essential for healthcare providers to be vigilant in monitoring liver function in patients on statin therapy including those on low doses with normal liver function test at onset of therapy. New and improved validated predictive scores for DILI can assist healthcare providers in providing personalized medical care involving individual patient's risk factors, medical history, and other medications being taken when deciding on the choice of statin and the appropriate monitoring schedule for liver function during statin therapy. Patient education is also

critical in recognizing potential symptoms of liver injury to ensure prompt notification of their healthcare provider. It is also essential for medical societies and organizations to review and update guidelines regularly to incorporate the latest evidence and best practices for monitoring adverse events related to statin therapy, including DILI. These measures will ensure the safe and effective use of statins while minimizing the risk of liver-related complications.

Abbreviations

ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ASCVD	Atherosclerotic Cardiovascular Disease
DILI	Drug Induced Liver Injury
GWAS	Genome-Wide Association Studies
INR	International Normalized Ratio
LDL	Low Density Lipoprotein
NAFLD	Non-Alcoholic Fatty Liver Disease
RUCAM	Roussel Uclaf Causality Assessment Method
ULN	Upper Limit of Normal

Conflicts of Interest

The authors declare no conflicts of interest.

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