Indian Journal of Pharmacy and Pharmacology 2023;10(3):241–243

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Pharmacy and Pharmacology

Journal homepage: https://www.ijpp.org.in/

Short Communication

Current views and prospects relating to the use of statins in patients with chronic liver disease and cirrhosis

Pavana Reddy[1], Stefy Jacob[2], Joshua George[2,*], M Sunitha[1], Vineeth Chandy[2]

[1]*Dept. of Clinical Pharmacy, T John College of Pharmacy, Doddakammanahalli, Karnataka, India*
[2]*Dept. of Pharmacy, T John College of Pharmacy, Doddakammanahalli, Karnataka, India*

ARTICLE INFO

Article history:
Received 13-09-2023
Accepted 25-09-2023
Available online 14-10-2023

Keywords:
Chronic liver disease (CLD)
Confidence interval (CI)
Creatine kinase (CK)

ABSTRACT

The objective of this study is to examine the existing evidence concerning the utilization of statins in individuals diagnosed with chronic liver disease and cirrhosis. Chronic liver diseases, such as cirrhosis and hepatocellular carcinoma, present substantial challenges to public health worldwide. The use of statins in these conditions has been a subject of concern due to potential liver injury risks. However, recent evidence from pre-clinical and clinical studies suggests that statins may have positive effects on disease progression, portal hypertension, and hepatocellular carcinoma prevention. These cholesterol-lowering drugs exhibit pleiotropic effects, including anti-inflammatory, anti-fibrotic, and antiangiogenic properties, which contribute to their potential benefits in chronic liver disease. While further research and randomized controlled trials are needed, statins offer a promising therapeutic avenue to prevent disease progression and improve outcomes in patients with chronic liver diseases.

Despite the global burden of chronic liver diseases and the limited availability of effective medications, statins have emerged as potential agents to address these conditions. Their primary cholesterol-lowering effect is complemented by additional mechanisms that positively impact inflammation, fibrosis, endothelial function, thrombosis, and coagulation. Although concerns persist regarding their hepatotoxic risks, studies have demonstrated the potential of statins to reduce the risk of disease progression, hepatic decompensation, hepatocellular carcinoma development, and mortality. Nonetheless, further large-scale randomized controlled trials focusing on clinical endpoints are necessary to ascertain the efficacy and safety of statin treatment in chronic liver diseases. Overall, statins hold promise as a valuable addition to the treatment armamentarium for chronic liver diseases, warranting further investigation and consideration in clinical practice.

1. Introduction

Chronic liver disease is a progressive deterioration of liver functions. Liver functions include the production of clotting factors and other proteins, detoxification of harmful products of metabolism, and excretion of bile.[1]

Chronic liver disease (CLD) is defined as a progressive degradation of liver functions lasting more than six months, including clotting factor synthesis, other protein synthesis, detoxification of toxic metabolic products, and bile excretion. CLD is a continual process of liver parenchymal inflammation, destruction, and regeneration that leads to fibrosis and cirrhosis. Chronic liver disease has a wide range of aetiologies, including toxins, long-term alcohol addiction, infection, autoimmune diseases, and genetic and metabolic problems.[1]

Cirrhosis is the terminal stage of chronic liver disease, characterized by disruption of hepatic architecture, the creation of extensive nodules, vascular reorganization,

* *Corresponding author*.
E-mail address: pr811150@gmail.com (J. George).

https://doi.org/10.18231/j.ijpp.2023.040

neo-angiogenesis, and extracellular matrix deposition. The recruitment of stellate cells is the basic process of fibrosis and cirrhosis at the cellular level.[2]

Statins have anti-inflammatory, proapoptotic, and antifibrotic actions in addition to cholesterol-lowering effects and it has been postulated that statins may play a role in non- alcoholic steatohepatitis (NASH). In this review, we present an overview of current evidence on the use of statins to treat or mitigate NASH.[3]

2. Discussion

The most commonly reported side effects during statin therapy are relatively mild and are often described as transient gastrointestinal symptoms (diarrhoea, abdominal pain, flatulence and constipation), headache and rash. Muscle damage, liver damage and new diabetes are proven side effects of statin therapy.[4–6]

Plasma levels of statins have been considered an index of their potential side effects and depend on several factors:

1. Statin dose: High-intensity statin therapy reduces cardiovascular events more than equivalent low-intensity therapy, but the safety of initial use is unknown. On this topic, a meta- analysis showed that high-intensity statin therapy increased aminotransferase elevations [relative risk = 3.10; 95% confidence interval (CI): 0.88–7.85] compared with lower intensity statin therapy. Based on clinical trials, the authors conclude that aggressive statin therapy increases aminotransferase levels more than lower intensity.
2. Type of statin: Nezasa et al showed in a rat model that hepatocytes take up rosuvastatin more selectively and efficiently than simvastatin. A possible reason for this finding is that rosuvastatin requires an anion transporter to enter cells, similar to pravastatin, another hydrophilic statin. This may be due to its higher lipophilicity, and in this way, it is taken up in the liver and extrahepatic tissues in the same way as other lipophilic statins such as atorvastatin and Fluvastatin. In the meta-analysis mentioned above, evaluating the different effects of hydrophilic and lipophilic statins, higher intensity treatment based on the former showed an increased risk of aminotransferase elevations, while those using lipophilic statins did not. Regarding the levels of creatine kinase (CK), they did not increase when hydrophilic statins were evaluated, while lipophilic statins showed an increased risk with more effective therapy. Therefore, aminotransferase elevations are likely to be more problematic when high-dose hydrophilic statins are prescribed, whereas CK elevations become problematic with equally aggressive lipophilic statin therapy. The cytochrome 4503A4 isoform usually has competitive inhibition with drugs at the enzymatic level and can alter the distribution of statins, increasing plasma concentrations and risk of side effects.[7]
3. Decreased metabolism and/or transport activity of statins: It is well known that cirrhosis significantly affects the pharmacokinetics of statins. Although the pharmacokinetics of simvastatin in cirrhotic patients has not yet been evaluated in any study, there are data on the use of other statins in Child-Pugh (CTP) class A and B patients. This last mechanism reduces liver uptake and increases blood levels of statins and increases the risk of side effects.[8]
4. Statin-related muscle adverse events ranged from 1-5% in controlled clinical trials and 11-29% in observational studies. Increasing evidence suggests that higher-dose statin therapy increases the risk of muscle damage (see Safety, Dosage of Statins). Statin-related muscle damage is also associated with drug interactions that increase serum concentrations of statins (see Safety, Drug Interactions). An N-1 study of eight patients with muscle pain during statin therapy showed that subjective side effects obtained from observational studies are full of bias.[9] The authors found no significant difference between statin and placebo in each patient's muscle pain when five patients returned to statin therapy. Muscle safety in cirrhotic patients was evaluated in three RCTs evaluating the effects of simvastatin on portal pressure and gastrointestinal bleeding.[9]

3. Conclusion

Similarly, and based on the safety study, we recommend that simvastatin 40 mg/day should not be given to patients with cirrhosis MELD score > 12 and/or CTP class CTP patients, as it may cause severe muscle damage.

In observational studies in large populations of patients with cirrhosis, statins have been associated with a reduced risk of liver failure, HCC, and death.[3]

Some Randomized controlled trails (RCT) in patients with cirrhosis and portal hypertension showed that statins lowered portal pressure, possibly through hepatic resistance.[10]

For these reasons, more RCTs in larger numbers of patients with severe clinical outcomes using different statins and different doses should be conducted before approving statins in patients with CTP class A/B cirrhosis to prevent liver-related morbidity and mortality.[11]

4. Source of Funding

None.

5. Conflict of Interest

None.

References

1. Sharma A, Nagalli S. Chronic Liver Disease. and others, editor. Stat Pearls Publishing; 2022.
2. Vargas JI, Arrese M, Shah VH, Arab JP. Use of statins in patients with chronic liver disease and cirrhosis: current views and prospects. *Curr Gastroenterol Rep*. 2017;19(9):43.
3. Torres-Peña JD, Martín-Piedra L, Fuentes-Jiménez F. Statins in non-alcoholic steatohepatitis. *Front Cardiovasc Med*. 2021;8:777131.
4. Kassebaum NJ, Arora M, Barber RM, Bhutta ZA, Brown J, Carter A. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990- 2015: a systematic analysis for the Global Burden of Disease Study. *Lancet*. 2016;388(10053):1603–58.
5. Newman CB, Preiss D, Tobert JA, Jacobson TA, Page RL, Goldstein LB. Statin safety and associated adverse events: a scientific statement from the American Heart Association. *Arterios Thrombosis Vascular Biol*. 2019;39(2):38–81.
6. Aishwarya A, Terry O. Statins in Alcoholic and Non-Alcoholic Fatty Liver Disease and Chronically Elevated Liver Enzymes. *Int J Clin Med*. 2022;13(7):229–52.
7. Cardiovascular Diseases Fact Sheet; 2017. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/.Accessed.
8. Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. *Diab care*. 2007;30(3):734–77.
9. Sepanlou SG, Safiri S, Bisignano C, Ikuta KS, Merat S, Saberifiroozi M, et al. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study. *The Lancet Gastroenterol Hepatol*. 2017;5(3):245–66.
10. Abraldes JG, Vilarrupla AR, Graupera M, Zafra C, Calderó HG, García-Pagán J, et al. Simvastatin treatment improves liver sinusoidal endothelial dysfunction in CCl4 cirrhotic rats. *J Hepatol*. 2007;46(6):1040–6.
11. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, et al. Effect of two intensive statin regimens on progression of coronary disease. *New England Journal of Medicine*. 2011;365(22):2078–87.

Author biography

Pavana Reddy, Student https://orcid.org/0009-0007-3371-5423

Stefy Jacob, Student

Joshua George, Student

M Sunitha, HOD

Vineeth Chandy, Principal

Cite this article: Reddy P, Jacob S, George J, Sunitha M, Chandy V. Current views and prospects relating to the use of statins in patients with chronic liver disease and cirrhosis. *Indian J Pharm Pharmacol* 2023;10(3):241-243.