Review Article

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Atorvastatin on Treatment of Nonalcoholic Fatty Liver Disease Patients

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Non-alcoholic fatty liver disease (NAFLD) is a condition in which excess fat builds up in the liver, often related to obesity and insulin resistance, which can lead to inflammation and scarring of the liver tissue. While efforts have been made to develop effective treatments for NAFLD, the need for pharmaceutical interventions remains unmet. Large clinical trials investigating the association between statin use and NAFLD are scarce, leading to contradictory results. Statins play a crucial role in cholesterol synthesis in the liver. Several studies have demonstrated that statins possess anti-inflammatory, anti-thrombotic, and anti-fibrotic properties. These properties make statins potentially useful in preventing the progression of NAFLD from simple steatosis to more severe forms like non-alcoholic steatohepatitis (NASH) and fibrosis. The results indicate that statin use is associated with a lower prevalence of NASH and fibrosis and may have a preventive effect on NAFLD.

Key Words: *Nonalcoholic Fatty Liver Disease; Atorvastatin; Lipids; Oxidative Stress; Inflammation*

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a prevalent liver condition that it has emerged as a significant health concern worldwide, with its prevalence exceeding 25% globally.[1] It is characterized by the accumulation of fat in the liver, leading to liver dysfunction and an elevation of serum liver enzymes.[2] The necroinflammatory grades of NAFLD/NASH have been classified by Brunt et al. into three categories: grade 1, grade 2, and grade 3. This classification is based on various factors such as the extent of hepatocellular steatosis, ballooning and disarray, and the presence of inflammation, both intralobular and portal.[3] Dyslipidemia, or abnormal lipid levels, is frequently observed in patients with NAFLD, making the treatment of dyslipidemia a crucial aspect of managing this condition.[4] While efforts have been made to develop effective treatments for NAFLD, the need for pharmaceutical interventions remains unmet.[5] However, recent studies have suggested that statins, a class of drugs primarily used to lower cholesterol levels, may have potential benefits in reducing the risk and progression of NAFLD.[6]

NAFLD is a liver disease that occurs in individuals who do not consume significant amounts of alcohol. It is closely associated with obesity, insulin resistance, and metabolic syndrome.[7] The accumulation of fat in the liver can lead to inflammation and the development of NASH, a more severe form of the disease. NASH can progress to liver fibrosis, cirrhosis, and even hepatocellular carcinoma.[8] Dyslipidemia, characterized by elevated levels of triglycerides (TG) and low density lipoprotein (LDL) cholesterol, is commonly observed in patients with NAFLD. These abnormal lipid levels contribute to the progression of liver disease and increase the risk of cardiovascular events. Therefore, the management of dyslipidemia plays a crucial role in the overall treatment of NAFLD.[9]

Statins, also known as HMG-CoA reductase inhibitors, are widely prescribed medications for managing high cholesterol levels and reducing the risk of cardiovascular diseases. They work by inhibiting the enzyme HMG-CoA reductase, which plays a crucial role in cholesterol synthesis in the liver. Statins, including atorvastatin, are widely used for the treatment of dyslipidemia and pre-

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vention of cardiovascular events.[10] However, there has been some hesitation in prescribing statins to patients with NAFLD due to concerns about liver toxicity and the potential exacerbation of liver disease.[11] Experimental and clinical studies have demonstrated that statins possess anti-inflammatory, anti-thrombotic, and anti-fibrotic properties.[12,13] These properties make statins potentially useful in preventing the progression of NAFLD from simple steatosis to more severe forms like non-alcoholic steatohepatitis (NASH) and fibrosis. Despite the potential benefits of statins in NAFLD, the existing evidence on their hepatoprotective effects remains segmented and inconclusive.[14] Large clinical trials investigating the association between statin use and NAFLD are scarce, leading to contradictory results.[15] Moreover, concerns about potential hepatotoxicity, given that statins are metabolized in the liver, have raised questions about their safety in patients with chronic liver disease.[14] However, studies have shown that statins are safe even in individuals with NAFLD and elevated liver enzymes. Research has shown that atorvastatin, when used at low-to-moderate doses, is generally safe and well-tolerated in patients with NAFLD.[16,17] It has been found to effectively lower LDL cholesterol levels and improve lipid profiles. Moreover, atorvastatin has been associated with a reduction in liver enzyme levels, indicating a potential improvement in liver function. These findings suggest that atorvastatin may have beneficial effects on both dyslipidemia and liver disease in patients with NAFLD.[18,19]

The use of atorvastatin in NAFLD management offers several potential benefits. Firstly, atorvastatin has been shown to reduce cardiovascular events in patients with dyslipidemia.[20] Since NAFLD patients often have an increased risk of cardiovascular disease, the cardioprotective effects of atorvastatin are particularly relevant in this population.[21] Secondly, atorvastatin has been found to have anti-inflammatory properties, which may be beneficial in the context of NAFLD. Inflammation plays a crucial role in the progression of liver disease, and reducing inflammation can potentially halt or slow the progression of NAFLD to more severe forms such as NASH.[22] Furthermore, atorvastatin has been associated with a decreased risk of hepatocellular carcinoma (HCC) development in NAFLD patients. HCC is a primary liver cancer that can arise as a complication of advanced liver disease, including NAFLD. By reducing liver inflammation and improving liver function, atorvastatin may help prevent the development of HCC in high-risk individuals.[23]

While atorvastatin has shown promising results in NAFLD management, there are some important considerations when prescribing this medication. Firstly, the dosage of atorvastatin should be carefully selected to minimize the risk of adverse effects. Low-to-moderate doses have been found to be effective and safe in NAFLD patients, and higher doses should be avoided to prevent potential liver toxicity.[24,25]

Secondly, close monitoring of liver enzymes is recommended during atorvastatin treatment in NAFLD patients. This allows healthcare providers to assess the medication's impact on liver function and make any necessary adjustments to the treatment plan. Regular follow-up visits and laboratory tests can help ensure the safe and effective use of atorvastatin in NAFLD management.[26,27]

Queries of trials were conducted in Web of science, PubMed, Scopus, and Google scholar. The following search terms were used: "non-alcoholic fatty liver disease," "NAFLD," "non-alcoholic steatohepatitis," "NASH," "atorvastatin," "Lipitor," "Liptonorm". Only literature in the English language and published from 2010 to 2023 were screened for inclusion. participants of any age or gender with NAFLD /NASH were included based on the following criteria: 1) Participants who displayed hepatic steatosis with or without elevated levels of liver enzymes, as observed through imaging or liver biopsy. 2) Participants who exhibited hepatic steatosis without any indication of alcoholism, hemochromatosis, Wilson disease, viral hepatitis, autoimmune hepatitis, schistosomiasis, or steroid usage, as determined through imaging or liver biopsy. The criteria for exclusion encompass individuals who are afflicted with any form of secondary ailment, such as cardiovascular diseases, diabetes, metabolic syndrome, and others. Additionally, those who concurrently ingest supplements and other medications alongside atorvastatin are also excluded.

ATORVASTATIN AND GLUCOSE

In clinical study, it is widely acknowledged that statins play a critical and pivotal role in the realm of preventive medicine for individuals who find themselves at an elevated risk for metabolic diseases. It is important to note, however, that alongside the manifold benefits that statins offer, there exists a legitimate and valid concern pertaining to the potential connection between these medications and the occurrence of hyperglycemia, as well as the subsequent increase in the likelihood of developing new-onset diabetes mellitus (DM).[28,29] Through an analysis of both randomized controlled trials and observational studies, it has been established that there exists a notably higher incidence of new-onset DM in patients who are prescribed statins as opposed to their counterparts who are not. This finding is exceptionally critical, as DM is recognized as a prominent and influential risk factor for the onset of various metabolic diseases, which in turn can lead to a plethora of long-term complications. Furthermore, it is crucial to note that not only is DM a highly pertinent factor in the realm of metabolic diseases, but impaired fasting glucose and pre-diabetes also hold significant weight as metabolic risk factors of utmost importance.[30,31] currently, the available data on the longitudinal alterations in fasting glucose levels resulting from the administration of statins are inadequate. Moreover, it is important to note that there exists a myriad of statin variations, each exhibiting a unique chemical constitution and pharmacokinetic behavior. Consequently, the distinct statin types may potentially exert dissimilar influences on the metabolic processes associated with glucose within the

body.[32] In a research study involving 57 patients diagnosed with NAFLD and dyslipidemia, the findings indicated that the administration of atorvastatin 20 mg over a span of 30 weeks did not elicit significantly alterations in the levels of blood glucose.[33]

ATORVASTATIN AND LIPID PROFILE

Atorvastatin effectively decreases cholesterol levels within the body by employing a variety of intricate mechanisms. One of its key actions involves the inhibition of HMG-CoA reductase, an enzyme responsible for the synthesis of cholesterol, which ultimately results in a reduction of the intracellular stores of cholesterol.[34] Subsequently, through a complex cascade of molecular events, Atorvastatin stimulates the upregulation of LDL receptors. This heightened expression of LDL receptors enhances the clearance of cholesterol from the bloodstream, leading to a substantial improvement in the overall lipid profile. Thus, through this multifaceted approach, Atorvastatin effectively combats hypercholesterolemia and significantly ameliorates the lipid composition of the body. Consequently, this process aids in maintaining a healthier lipid profile.[35] Moreover, atorvastatin proves its efficacy in preventing lipid accumulation in hepatocytes, which are liver cells, through the activation of the protein kinase pathway via AMPK. This activation of the protein kinase pathway serves as a protective measure against the buildup of lipids in hepatocytes, ultimately leading to improved liver health. AMPK serves as a regulatory factor for numerous metabolic pathways, thus exhibiting potential as a therapeutic agent in conditions such as NAFLD, type 2 diabetes, and insulin resistance.[36,37] Another mechanism that can be attributed to the drug atorvastatin involves the intricate regulation of beta oxidation, which is primarily mediated by two key transcription factors known as peroxisome proliferator-activated receptor alpha (PPARa) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1a). These transcription factors play a crucial role in modulating the expression of various genes that are involved in the process of beta oxidation, thereby exerting a profound impact on lipid metabolism. The intricate interplay between atorvastatin, PPARa, PGC1a, and their target genes ultimately contributes to the pharmacological effects of atorvastatin in the context of lipid regulation. In the studies that were conducted on patients afflicted with NAFLD, it was observed that the utilization of atorvastatin, an anti-lipidemic medication, yielded noteworthy results (Fig. 1).[38-40] These studies encompassed a diverse group of patients, including 57 individuals suffering from both NAFLD and dyslipidemia, who were administered a dosage of 20 mg of atorvastatin for a duration of approximately 32.8±3.4 weeks.[33] Another group consisted of 151 patients diagnosed with either NAFLD or NASH, who were subjected to a higher dosage of 31 mg of atorvastatin for a period of one year.[41] Furthermore, a study comprising of 40 NAFLD patients were given a dose of 20 mg of atorvastatin for a span of three months,[42] while an additional 50 patients with NAFLD were prescribed a dosage of 40 mg of atorvastatin for a duration of eight months.[43] The outcomes of these studies demonstrated a clear correlation between the administration of atorvastatin and a reduction in levels of TG, LDL, and total cholesterol, accompanied by an augmentation in HDL.

ATORVASTATIN AND LIVER ENZYMES

In the investigations that were carried out on individuals afflicted with NAFLD/NASH, it was revealed that the utilization of atorvastatin at varying dosage levels of 20,[33,42] 31,[41] and 40[43] was found to be correlated with a noticeable reduction in the quantity of aminotransferases, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT), along with a marked amelioration in the condition of NAFLD. In the meantime, according to the findings derived from previous investigation, there exists a theoretical assumption that atorvastatin, owing to alterations in the composition of lipids within cellular membranes and the consequent modifications in their permeability, potentially triggers the release of hepatic enzymes into the circulatory system, consequently causing a rise in their concentration within the plasma.[44] Among the various categories

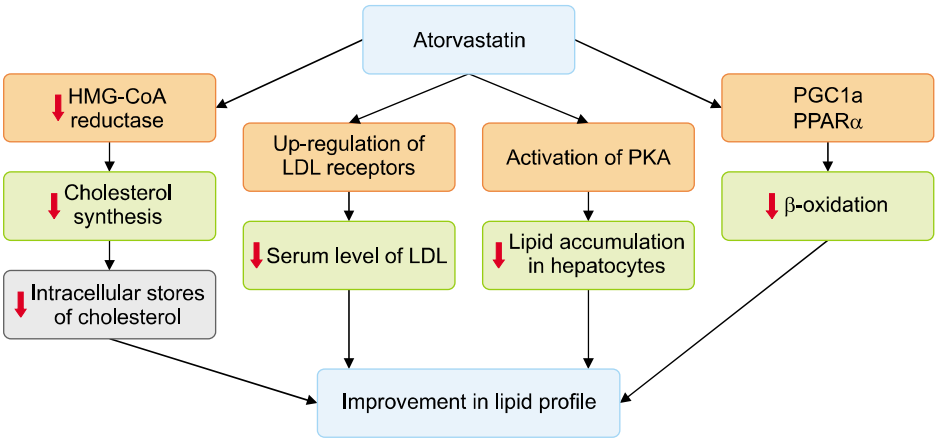

FIG. 1. Mechanism action of Atorvastatin on lipid profile.

of statins, it has been demonstrated in scientific studies that atorvastatin, a widely prescribed medication for reducing cholesterol levels in the body, can lead to the development of chronic liver damage due to its propensity to induce hepatotoxicity, which refers to the toxic effects on the liver (Fig. 2).[45,46]

ATORVASTATIN, LIVER STEATOSIS, NECROSIS, AND FIBROSIS

Atorvastatin exerts its beneficial effects on the oxidative stress induced by angiotensin II by means of inhibiting RhoA, a small GTP-binding protein that plays a crucial role in various cellular processes, and simultaneously enhancing the expression and activity of endothelial nitric oxide synthase (eNOS), an enzyme responsible for the production of nitric oxide, a potent vasodilator and anti-inflammatory molecule. Conversely, this medication also demonstrates its efficacy in ameliorating the detrimental consequences associated with fibrosis and cirrhosis through the inhibition of GTPase prenylation, a post-translational modification crucial for the localization and function of various proteins involved in cell signaling and cytoskeletal organization.[47-49]

The controversial nature of the effect of statins on liver fibrosis has been a subject of much debate within the scientific community. Numerous studies have investigated the potential impact of statins on liver fibrosis, yielding conflicting results. While some studies suggest that statins may have a beneficial effect on liver steatosis, potentially reducing the likelihood of disease progression to fibrosis, there are also opposing studies that argue against the role of atorvastatin in improving liver fibrosis. This discrepancy in findings highlights the complexity of the relationship between statins and liver fibrosis, necessitating further research to elucidate the true effects of this medication on hepatic fibrosis.[50-52] The discrepancy observed in the outcomes may potentially be attributed to the specific classification of statin utilized in the study, as well as the length of time for which it was administered (Fig. 3).[52] The findings of two separate investigations are as follows: the first study involved 57 individuals diagnosed with NAFLD who were administered a 20 mg dosage of atorvastatin for a duration of 32 weeks,[33] while the second study involved 151 patients who had both NAFLD and NASH and were given a 31 mg dosage of atorvastatin for a period of one year.[41] The results of these studies suggest that the utilization of atorvastatin leads to an enhancement in liver steatosis and fibrosis. However, it should be noted that no notable alteration in necrosis was observed.

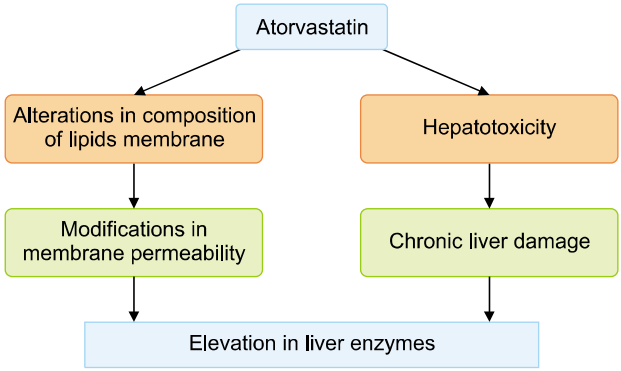

FIG. 2. Mechanism action of Atorvastatin on liver enzymes.

ATORVASTATIN AND LIVER INFLAMMATION

Atorvastatin has been shown to be highly efficacious in ameliorating hepatic inflammation by employing various intricate mechanisms. The beneficial effects of Atorvastatin in mitigating hepatic inflammation induced by NAFLD are achieved through its potent inhibitory action on leukotrienes, lipoxins, and lipoxygenases, as well as its ability to impede the synthesis of eicosanoids, which are known to play pivotal roles in the inflammatory processes.[53,54] In an alternative mechanism, the anti-inflammatory effects of atorvastatin are manifested through its inhibitory action on the production of tumor necrosis factor alpha (TNF-a), a potent pro-inflammatory cytokine, thereby effectively diminishing the inflammatory response.[55] Additionally, atorvastatin exerts its anti-inflammatory influence by impeding the activity of transforming growth factor beta (TGF-b), a multifunctional cytokine involved in various physiological processes, including inflammation. Through its inhibitory effects on these key mediators of inflam-

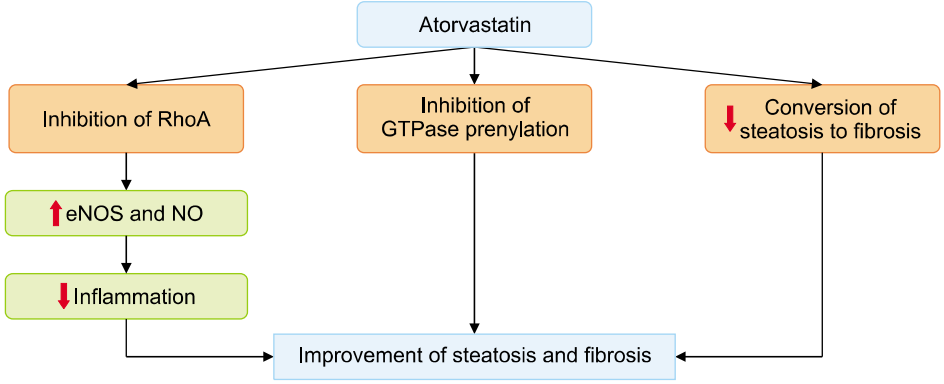

FIG. 3. Mechanism action of Atorvastatin on steatosis and fibrosis.

mation, atorvastatin effectively mitigates the inflammatory cascade, leading to a reduction in tissue damage and improved clinical outcomes (Fig. 4).[22,56] The outcomes derived from the conduction of two separate and distinct research studies, the first of which involved a sample size of 57 patients diagnosed with NAFLD who were administered a dosage of atorvastatin 20 mg over the course of 32.8±3.4 weeks,[33] and the second study which encompassed a study of 40 patients afflicted with NAFLD who were subjected to a treatment regime involving atorvastatin 20 mg for a duration of 3 months,[42] serve to demonstrate, with a certain degree of certitude, that there was a noticeable and statistically significant amelioration in the inflammatory condition of the liver, as well as in the overall CRP index.

ATORVASTATIN AND STRESS OXIDATIVE

Although statin possesses antioxidant characteristics, it induces harm to various tissues, including the liver and kidney, as a result of oxidative stress. Consequently, the impacts caused by the administration of atorvastatin exhibit variability contingent upon the particular target tissue under consideration.[57] Broadly speaking, the mechanism of action of statins lies in their ability to impede the generation of reactive oxygen species (ROS) while concurrently augmenting the levels of nicotinamide adenine dinucleotide (NADH), thereby mitigating the deleterious effects of oxidative stress. Additionally, it is worth noting that this pharmaceutical agent exerts a favorable influence on the process of lipid peroxidation, as well as on the levels of adiponectin. Thus, it can be surmised that the multifaceted properties of statins contribute to their efficacy in combating oxidative stress and related pathophysiological processes (Fig. 5).[58] In the research investigations carried out on individuals diagnosed with NAFLD, it has been demonstrated that the utilization of atorvastatin in a dosage of 20 mg over a period of three months,[42] as well as the administration of atorvastatin at a dosage of 40 mg for a duration of eight months,[43] is positively correlated with a reduction in the levels of catalase, glutathione reductase, malondialdehyde (MDA), and paraoxonase 1, respectively.

While the current evidence supports the use of atorvastatin in NAFLD management, there is still a need for further research. Randomized clinical trials of adequate size and duration are necessary to determine the long-term efficacy and safety of atorvastatin in NAFLD patients. Additionally, more studies are needed to investigate the specific mechanisms by which atorvastatin exerts its beneficial effects on NAFLD and its related complications.

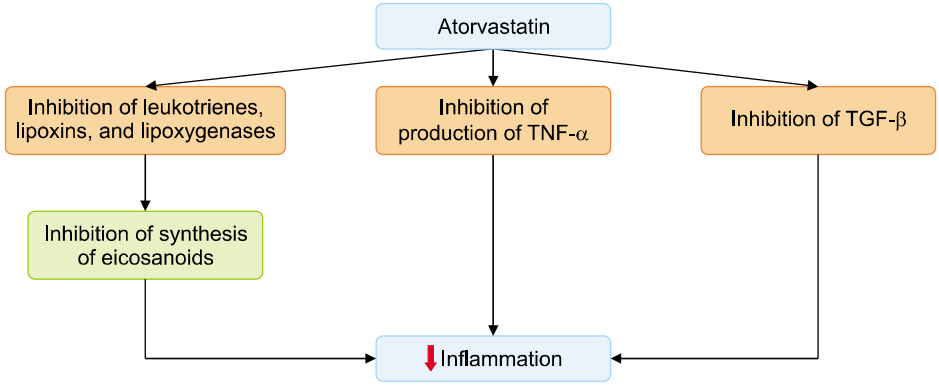

Fig. 4. Mechanism action of Atorvastatin on liver inflammation.

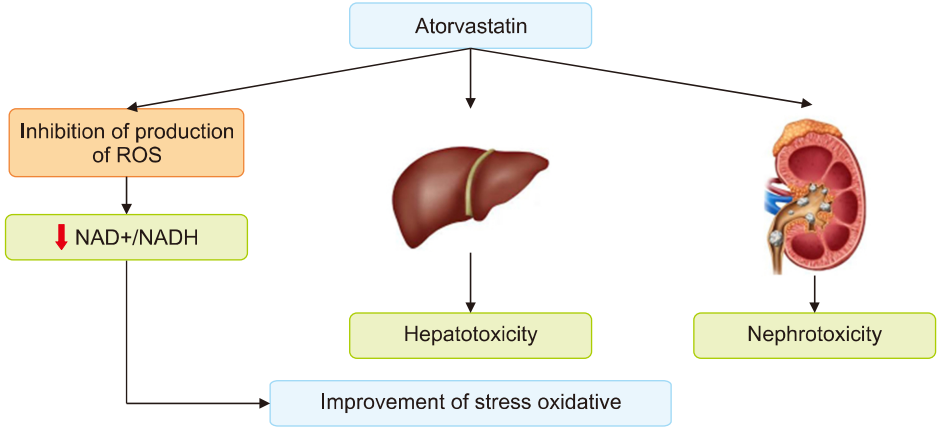

Fig. 5. Mechanism action of Atorvastatin on stress oxidative.

CONCLUSION

Atorvastatin, a commonly prescribed statin, has shown promise in the management of NAFLD. It effectively lowers LDL cholesterol levels, improves dyslipidemia, and may have additional benefits such as reducing liver inflammation and the risk of hepatocellular carcinoma. While atorvastatin is generally safe and well-tolerated in NAFLD patients, careful dosage selection and regular monitoring of liver enzymes are essential. Future research is needed to further explore the efficacy and mechanisms of action of atorvastatin in NAFLD management. By integrating atorvastatin into the treatment plan for NAFLD patients, healthcare providers can address both dyslipidemia and liver disease, ultimately improving patient outcomes and reducing the risk of cardiovascular events and liver-related complications. Based on the findings of the four aforementioned studies, a general conclusion can be drawn that the administration of atorvastatin in lower dosages over an extended duration yields more favorable outcomes compared to higher dosages.

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CONFLICT OF INTEREST STATEMENT

None declared.

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