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Statins in Cirrhotic Portal Hypertension – A Brief Review

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Abstract

Nowadays the cirrhosis physiopatology is being deeply studied and new pharmacology approach comes with new perspective of changing natural history and initial steps of the disease. The statins have many properties in this sense. These drugs have demonstrated effects improving portal hypertension, liver functions, hepatocellular carcinoma with few side effects. Its action mechanism happens predominantly in intrahepatic environment, what seems very attractive. Some studies were conducted in animals and very few in human beings. This brief review aim to address advantages of the use of statins in liver disease. One question still open is which statin is the best in liver disease and which population of cirrhotic profit the most of the drug.

Keywords: Portal hypertension; Statins; Cirrhosis

Introduction

The new therapeutic targets in chronic liver disease are, mainly, fibrogenesis and Intrahepatic Vascular Resistance (IHVR), acting in many levels of portal hypertension (PH) pathophysiology. These targets are well sustained once besides improving portal hypertension directly, also can act in perfusion and, consequently, liver functions. The augmented IHVR is a complex mechanism [1] and with many steps, potentially attainable by drugs and new therapeutic measures. The endothelial dysfunction present in cirrhosis results in imbalance between vasodilators and vasoconstrictors besides the inflammatory and pro thrombotic roles [1]. In this context, statin seems a very attractive option since can interacts at the endothelium without the deleterious systemic effects seen with angiotensin converting enzyme inhibitors and others vasodilators [2]. The systemic effect of vasodilation is poorly tolerated and frequently leads to the drug suspension [3,4].

Materials and Methods

A search in Embase, Scielo, Cochrane, PubMed and CINAH databases for the last 5 years, was using the following keywords: statins, cirrhosis and portal hypertension. The studies were chosen by the relevance of the research, basic research, and clinical trials.

Statins

This class of drugs have been prescribed as a lipid lowering medication for decades but, are now well recognized by its mainly effects in endothelium. Statins acts in endothelium phenotype improving its properties and resulting in antioxidative, antiproliferative, antiinflammatory and antithrombotic effects [5]. Anti-oxidative stress molecules are found lacking in hepatic cirrhosis [1] as like the tetrahydrobiopterin, responsible cofactor to regulate eNOS activity increasing availability of NO. Superoxide dismutase (SOD), an enzyme that catalyses free radicals of oxygen, is also diminished in hepatic cirrhosis [1]. Many drugs are available and being evaluating in nowadays for the purpose of restore these factors likes fenofibrate that acts by other mechanism, through the activated proliferative peroxissome alpha receptor (PPAR alpha) [6], in the oxidative stress mechanisms; antibiotics, like rifaximin, largely used in gastroenterology and hepatology, that decreases endotoxin levels; All of these drugs can potentially decrease Hepatic Venous Pressure Gradient (HVPG).

In the context of collateral formation and neoangiogenesis stimulated by VEGF and PEGF [7], its antagonists seems to decrease PH lowering splanchnic vasodilation and formation of portosystemical collateral vessels but have serious adverse effects, not tolerated or not permissible in cirrhotic patients.

Recently, the non cirrhotical portal hypertension was studied and its pathophysiology demonstrated to be different from cirrhotic one. The role of statins, atorvastatin, in cirrhotic portal hypertension was proved to be different than the one in non-cirrhotic portal hypertension. Statins inhibit non-canonical Hedgehog signalling and cirrhotic portal hypertension [5]. Atorvastatin for a short period can blunt neo angiogenesis in cirrhosis by non-canonical HedgeHoc signalling meanwhile in non-cirrhotic portal hypertension statin increases systemic and splanchnic neo angiogenesis by canonical way [8].

Two randomized controlled trials showed the reduction of hepatic venous pressure gradient (HVPG) by simvastatin 40 mg. Abraldes et al. first performed a randomized controlled trial for one-month of simvastatin and evaluated the hemodynamic response. The decrease was 8.3% (± 12.2%), p=0.041 in patients treated with simvastatin [6]. The decrease to target hemodynamic response was observed in 32% of cirrhotic patients. Another randomized controlled trial was conducted for three months 40 mg simvastatin and the decrease in HVPG was 15% (IQR 17), (p=0.02), demonstrated in 55% of patients in statin arm [7].

Simvastatin with an increased post translational regulation of nitric oxide synthase can selectively increase NO in intrahepatic milieu without the adverse effects of the vasodilators, reducing the portal pressure. Statins can act in pathways by blocking HMG-coA reductase, like RhoA/RhoA kinase besides the canonic HedgeHoc pathway, non canonic HedgeHoc pathway and nitric oxide synthase enzyme modulating the IHVR [8]. Moreover, atorvastatin not only reduces IHVR but also neo angiogenesis and collaterals flow [9]. Finally, atorvastatin decreases fibrogenesis, hepatic resistance and shunt flow in cirrhotics models in rats [9].

The first study in humans showed that simvastatin has decreased

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HVPG in 32% of patients [10]. The effect magnitude was moderated, with a decrease of 10% in 40% of the patients and ≥ 20% or <12 mm Hg in a third of the patients. Moreover, the benefits could be observed even in beta blockers users, addictive effect. The HVPG reduction was concomitant with improvement of hepatic perfusion and hepatic function (mechanism evaluated through indocyanine green) [10]. The study with three months of simvastatin also showed some gain in liver function in parallel of portal hypertension and portosystemic collaterals flow reduction [11].

Statins can reduce oxidative stress and inflammation in vessel walls, having antithrombotic and anti-inflammatory properties improving pathological endothelial phenotype. Therefore, statins may affect the reversible component of pH [12].

Increase in the production of NO is mediated by the activation of kinase protein AKT dependent of phosphatidyl inositol-3 kinase leading to phosphorylation of endothelial NO synthase in Ser1177 which induces the increase of the eNOS function [3]. There are other post translational regulations with the increase of translational nuclear factor "*Krupper-like 2*" (KLF-2), important to the transcription of endothelium protecting genes. This way, statins improve the flow mediated by vasodilation of intrahepatic vascularization in and reduces the post prandial HVPG [4,9,10].

Statins reduce the oxidized LDL and alpha-TNF. Oxidized LDL has many deleterious effects, also is an agonist of endothelin production, and when decreased ameliorate endothelium function.

Atorvastatin attenuates hepatic fibrosis in rats submitted to bile duct ligation [13]. In the established cirrhosis, atorvastatin decreased the proliferation and apoptosis of myofibroblastic HSC and the expression of profibrotic kitokines without significative effects in inflammation. Atorvastatin also interferes with the Rho/Rho a kinase, inhibiting and decreasing vascular tone for the complex mechanisms that involve its regulation. The most important conclusion of this study was, then, that atorvastatin can attenuates HSC activation and despite a week of atorvastatin didn't affect collagen content may interfere in HSC and pro-fibrotic cytokines. These beneficial effects of atorvastatin in animal models need to be confirmed in human beings [14].

Statins modulates negatively caveolin-1 levels regulating its expression and interaction with eNOS [12]. Inflammatory mechanism of action of statins is being better understood nowadays and this inflammatory stimulus induces the expression of platelet adherent molecules (VCAM 1 and Icam 1) which recruit immune cells to the vessel wall [12].

A healthy endothelium produces thrombomodulin and tissue plasminogen activator (tPA) while inflammatory stimulus decreases thrombomodulin and increases pro-clotting factors. Recent studies show that statins stimulate production of endothelium protecting nuclear factors such as "Kruppel-Like factor 2" (KLF-2) and Peroxisome proliferator-activated receptors (PPARs) [15,16].

Recently, another study showed that statins blunt the Rho A/Rho A Kinase pathway in myofibroblast hepatic stellate cells. This pathway also interferes with Hedgehoc canonical and non-canonical signalling. These mechanisms are envolved in neoangiogenesis, a crucial step in portal hypertension. The central issue in this study was the discovery of two different mechanisms of neoangiogenesis in portal hypertension, in cirrhotic and non-cirrhotic ones. The statins decreases portal hypertension and shunts in cirrhotic liver but not in non-cirrhotic portal hypertension [6].

Another issue concerned in statin effect on liver disease may be also the ethiology and stage of cirrhosis. The atorvastatin and rosuvastatin did not inhibited fibrosis after thioacetamide induced cirrhosis in rats [17]. The potential anti-oxidant and anti-fibrotic roles of these drugs were not demonstrated. Although the thioacetamide by oxidative stress results in liver cirrhosis, it is now evident that many biological effects, mainly pleiotropic ones may lead to clinical benefits. The NO endothelium production in cirrhosis is clearly associated with the hemodynamic response observed in statin treated patients, an event not present in all stages of cirrhosis.

Conclusion

In conclusion, statins can reduce portal hypertension and ameliorate sinusoidal dysfunction among others benefits. It seems that this class of drugs can even improve prognosis in cirrhosis [18]. More studies are still necessary to address the benefits of statin in cirrhosis as well as to evaluate which statin is better in which cirrhosis context.

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