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IMPROVEMENT OF HEPATIC BIOAVAILABILITY AS A NEW STEP FOR STATIN FUTURE

Type:

Review paper (After Acceptance of EiC)

Running head:

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Statins (HMG-CoA reductase inhibitors) belong to the group of highly efficient pharmacological agents used for reducing blood cholesterol level and prevention/treatment of cardiovascular disease. Adverse reactions during statin treatment affect quite significant numbers of patients (reportedly from 5% to 20%) with more side effects occurring at higher doses. Reduced statin dosaging can be achieved by an improved bioavailability of statins which is fairly low due to poor aqueous solubility, low permeability and high molecular weight of some members belonging to the statin family. Moreover, since hepatic cholesterologenesis is a main target of statin action and extrahepatic inhibition of HMG-CoA reductase has no known therapeutic benefits, hepatic bioavailability, in our opinion, becomes a new important modality of statins maximizing their potential effect on plasma lipid profile and diminishing their extra-hepatic toxicity. Therefore efficient delivery systems of statins into hepatocyte need to be developed and introduced.

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ABSTRACT

Statins (HMG-CoA reductase inhibitors) belong to the group of highly efficient pharmacological agents used for reducing blood cholesterol level and prevention/treatment of cardiovascular disease. Adverse reactions during statin treatment affect quite significant numbers of patients (reportedly from 5% to 20%) with more side effects occurring at higher doses. Reduced statin dosaging can be achieved by an improved bioavailability of statins which is fairly low due to poor aqueous solubility, low permeability and high molecular weight of some members belonging to the statin family. Moreover, since hepatic cholesterologenesis is a main target of statin action and extrahepatic inhibition of HMG-CoA reductase has no effect on plasma lipids, hepatic bioavailability, in our opinion, becomes a new important modality of statins maximizing their potential effect on plasma lipid profile and diminishing their extra-hepatic toxicity. Therefore efficient delivery systems of statins into hepatocyte need to be developed and introduced.

Uses of nano-emulsifying statin delivery systems which may include vectors of intrahepatic transport, in particular lycopene are discussed. As a proof of concept, some preliminary results revealing effect of lycopene-containing nano formulation of Simvastatin (designated as Lyco-Simvastatin) on LDL in mildly hypercholesterolemic patients are shown.

BACKGROUND

Cholesterol is an essential component of every living eukaryotic cell required for the formation of cell membranes and cellular organelles, serving as well as a major metabolic precursor of all steroid hormones, bile acids and vitamin D (1). Over 90% of cholesterol is located in the tissues and organs of an animal body, whereas 7-10% is associated with plasma and blood cells. Since cholesterol is a highly insoluble substance it is transported in blood by particles, called lipoproteins, which are classified according to their density. Lipoproteins of low density (LDL) are known to be a major transport form of cholesterol in human blood (2). An overwhelming number of epidemiological studies suggest that elevated levels of LDL and total cholesterol in blood are linked to increased incidences of cardiovascular disease and higher mortality of cardiovascular patients (3, 4). On the other hand, reduced LDL and total cholesterol values confer a lower occurrence of atherosclerosis, stroke and myocardial infarction in patients with atherosclerosis and peripheral artery disease (5, 6, 7). Therefore, reduction of blood cholesterol, especially its LDL fraction, represents the most popular and modern approach in the prevention and pharmacological management of cardiovascular disease (8, 9).

STATINS

Approximately 80% of cholesterol in human blood originates from the liver (10). Therefore a search for effective pharmacological inhibitors of hepatic lipogenesis initiated decades ago remains the most effective strategy in the prevention and treatment of hypercholesterolemia and atherosclerosis. Screening of different xenogenic compounds resulted 30 years ago in the discovery of selective inhibitors of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase), a rate-limiting enzyme of cholesterol biosynthetic pathway in the liver (11). Notably, pharmacological inhibition of any other enzyme belonging to the cholesterol biosynthesis pathway in the liver is not as effective in terms of the cholesterol reduction in blood (12). Subsequently, a new class of pharmacological compounds called statins emerged. This group recently includes lovastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin and atorvastatin. All of them have a closely related chemical structure and work exclusively by activation of the hepatic clearance of plasma lipoprotein via a LDL-receptor pathway and further elimination of cholesterol from the human body with bile (11, 12, 13). Thus, the reduction of cholesterol in the blood of statin-treated patients is a strictly liver-mediated phenomenon (14). It has to be emphasized that HMG-CoA reductase, the only known molecular target of statins mediating their effects on lipid profile, is a liver-specific enzyme poorly expressed in other tissues (15). Despite undisputable health

benefits of the statin treatment proven in hundreds of research projects (reduction in heart attack/sudden cardiac death incidence by 60%, and strokes by 17%), there are some significant concerns related to their long-term use in clinical practice (16). It is believed that poor compliance and insufficient persistence in statin treatment does not confer measurable health benefits (17). However long-term intake of statins is associated with significant side effects. Adverse reactions during statin treatment affect quite significant numbers of patients (reportedly from 5% to 20%) with more side effects occurring at higher doses (18). Myopathies, memory impairment, neuropathies, increased risk of type 2 diabetes, elevated liver enzymes, general weakness and depression are reported in statin-treated patients (19). Among them, muscle damage leading in extreme cases to fatal rabdomyolysis is considered to be the most severe side effect of statin therapy (20, 21). It has to be emphasized that toxic effects of statins develop in a strictly dose-dependent manner and often subside when the dose is reduced. Therefore, an avoidance of unnecessarily intense treatment schedules and targeting the statin delivery to the liver might be very useful in the prevention of statin toxicity.

BIOAVAILABILITY OF STATINS

Reduced statin dosaging can be achieved by an improved bioavailability of statins which is fairly low due to poor aqueous solubility, low permeability and high molecular weight of some members belonging to the statin family.

As an example, the bioavailability rate for lovastatin is astonishingly low, approximating 5% only, whereas the reported value for simvastatin is much higher, reaching up to 60% (22). Although limited aqueous solubility of statins is considered to be an important cause of their low bioavailability, a solubility enhancement, as well as maximizing of intestinal absorption of statins used as single approach, is not likely to be a successful strategy. High concentration of statins in systemic circulation may aggravate the statin side effects and toxicity in the long term.

It can be assumed, that since hepatic cholesterologenesis is a main target of statin action, an efficient delivery systems of statins into hepatocyte needs to be developed. Therefore hepatic bioavailability becomes a new important modality of statin action in the human body maximizing their potential effect on plasma lipid profile and diminishing their extra-hepatic toxicity.

INTRAHEPATIC AVAILABILITY AS A KEYSTONE FEATURE OF STATIN ACTION

Occurrence of statins in the systemic circulation upon absorption does not necessarily translate into an immediate lipid-lowering effect. At the onset of their action, statins have to become available for binding with HMG-CoA reductase inside hepatocytes. However, statins tend to be widely distributed among different internal organs and tissues (liver, spleen, adrenal glands, adipose tissue and muscles) after absorption (23). Once again, the liver is a

main target organ for HMG-CoA reductase inhibitors, and statin action in non-hepatic tissues has no known therapeutic benefits, minimizing deposition of statins in extra-hepatic tissues as well as enhancing statin delivery to the liver would be very beneficial for clinical practice. First-pass uptake of statins by hepatocytes is reported to be mediated by different mechanisms including a passive diffusion and an active, carrier-mediated transport through hepatocyte membrane with organic anion transport polypeptide-C is thought to be essential for hepatocellular delivery of hydrophilic statins (22, 24). Strikingly, rosuvastatin, a known champion of hepatoselectivity among statins, whose intrahepatic delivery rate reaches 90% of the dose absorbed in the intestine, has the most prominent effect on plasma LDL as well as remarkably low toxicity (22).

Taking everything into consideration, it can be stated that an ideal statin delivery system has to meet at least two basic requirements. Firstly it has to provide efficient transport of statins through a gastrointestinal barrier and secondly it has to be capable of effective intrahepatic delivery of the drug. Moreover, there is a huge and yet poorly explored promise in use of endogenous receptor-mediated hepatic pathways to promote intrahepatic delivery of pharmaceuticals. Various receptors expressed on hepatocyte membranes have extreme selectivity and efficiency in the internalization of different ligands as opposed by less efficient passive and active diffusion of xenobiotics through hepatocyte membrane. Therefore construction of

microparticles containing a xenobiotic compound bound to the ligands of receptor-mediated intrahepatic uptake may represent a new strategy in enhancing hepatoselectivity of statins.

From this standpoint a novel statin delivery system, designated as Lycostatin, was developed in our work (25). Lycostatin is a new formulation of statins in which the HMG-CoA reductase inhibitor, in particular Simvastatin (named Lyco-Simvastatin), is incorporated into a microemulsifying system using spray drying, ultrasound, supercritical CO_2 (26). This system contains lycopene, a hydrophobic compound, which is used not only as a core-forming agent, but also as a vector with high tropism to hepatocytes, which are known to express abundantly a carotenoid receptor. In addition it contains amphiphilic phosphatydilcholine as a chaperone for lycopene, which also has hydrophilyzing as well as emulsifying properties and increases thereby intestinal absorption. In a water-free environment Lyco-Simvastatin is a composition of nano-sized lycosome particles. In experimental settings, the solubilized lycosome particles have an enhanced intestinal absorption rate and ability to bind hepatocyte membranes as compared to unmodified simvastatin (Petyaev IM et al, unpublished observation). The preliminary clinical results for Lyco-Simvastatin use are shown in Figure 1. As can be seen from our preliminary results (Figure 1), Lyco-simvastatin has superior activity in reducing LDL

levels in patients with hypercholesterolemia at the same dosage level (20 mg daily) as compared to the unmodified Simvastatin (P=0.0049).

Although further research related to pharmacology of Lyco-Simvastatin (as well as other lycosome-formulated statins) still needs to be done, these results allow to assume that higher functional activity of Lyco-Simvastatin could be attributable to an enhanced hepatic delivery of the drug arising from the specifics of the nanoparticles composition used. The interface area of Lycosome-formulated statin microparticles contains lycopene, a carotenoid utilizing a unique transport system inside the human body. It is well acknowledged, that upon absorption lycopene crystals and/or lycopene-containing nanoparticles (lycosomes) become incorporated into chylomicrones to be distributed in the human body by lymph and blood flows (27). Inside the liver the lycosome-containing chylomicrones are likely to undergo a dual receptor-mediated uptake. Since lycosome-containing chylomicrons include in their core lycopene, a powerful ligand for carotenoid receptors, expressed by hepatocytes, they become more easily internalized by these cells via a carotenoid receptor mechanism, promoting thereby intrahepatic delivery of Lycosome-formulated statins. Besides the carotenoid receptor, the enhanced hepatocellular delivery of Lycostatins can be confidently explained by LDL-receptor mechanism, which represents, in our opinion, a second pathway of the intrahepatic uptake. It is well known, that chylomicrones and products of their enzymatic degradation (LDL and VLDL)

are transported inside hepatocytes using LDL-receptor mediated by ApoB, an intrinsic component of low density lipoprotein particles (28).

CONCLUSION

Discovery of statins and their further development started with scrupulous investigation and subsequent chemical modifications of compactin, a single naturally occurring small molecule produced by fungus from the *Penicillium* family (29, 30). In recent times the search for new statins has been virtually exhausted since computational chemistry does not predict any new statin derivate showing inhibitory activity towards HMG-CoA reductase (31). Therefore, the developments in pharmacology of hypercholesterolemia will be limited in the foreseeable future to already known statins, while optimization of their delivery systems and bioavailability may offer new therapeutic benefits. However, a projected use of statins will likely to grow over next decades as new indications for their use become substantiated (18, 32).

In these terms development of statin formulations with an increased hepatic bioavailability would be a significant step forward in the treatment of cardiovascular disease. Incorporation of simvastatin in the lycopene-containing microparticles, promoting their enhanced absorption and subsequent incorporation in chylomicrones with further hepatic intake via

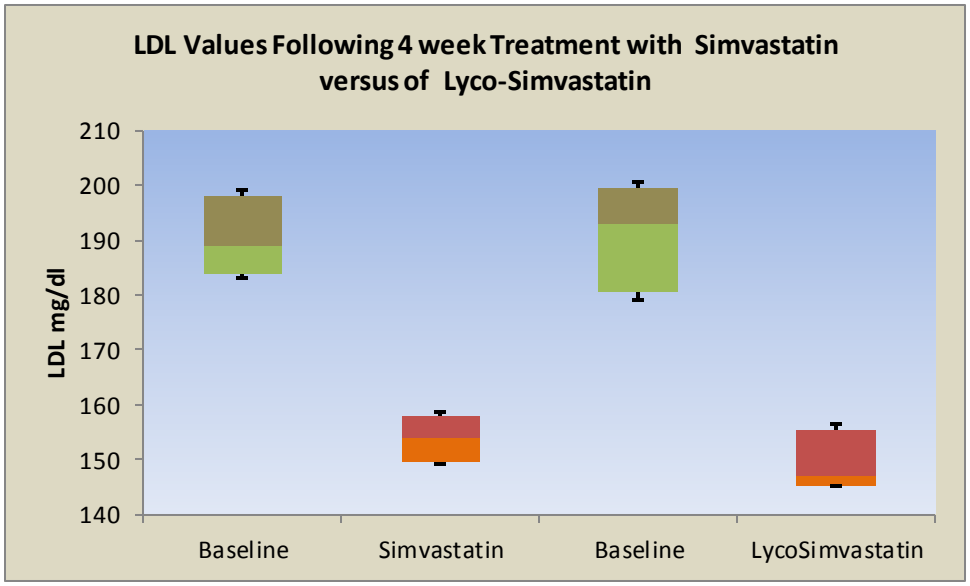
dual carotenoid/LDL receptor mechanism ensures targeted hepatic delivery of the drug to the liver. It is possible that other vectors promoting an efficient hepatic delivery can be used for new statin formulations with an enhanced therapeutic efficiency. Redirecting a drug flow to the liver allows not only statin dose reduction but also minimizes exposure of the tissues vulnerable to statin action (muscles, nerve tissue etc.) thereby reducing adverse effects. This would help to expand the use of this drug to the broader population to further reduce the prevalence of cardio-vascular disease and other clinical complications of atherosclerosis.

REFERENCES

1. Coyan FC, Loussouarn G. Cholesterol regulation of ion channels: Crosstalk in proteins, crosstalk in lipids. Channels (Austin). 2013 Oct 2;7(6). [Epub ahead of print]
2. Poirier S, Mayer G. The biology of PCSK9 from the endoplasmic reticulum to lysosomes: new and emerging therapeutics to control low-density lipoprotein cholesterol. Drug Des Devel Ther. 2013 Oct 4;7:1135-1148.
3. Mark L, Paragh G, Karadi I, Reiber I, Pados G, Kiss Z. How can we further improve the LDL-cholesterol target level achievement rate based on the Hungarian MULTI GAP 2011 study results and considering the new European dyslipidemia guidelines? Arch Med Sci. 2012 Sep 8;8(4):608-13.
4. Webb J, Gonna H, Ray KK. Lipid management: maximising reduction of cardiac risk. Clin Med. 2013 Dec;13(6):618-20.
5. Katsiki N1, Mikhailidis DP, Athyros VG, Hatzitolios AI, Karagiannis A, Banach M. Are we getting to lipid targets in real life? Arch Med Sci. 2010 Oct;6(5):639-41.
6. Aronow WS. Peripheral arterial disease of the lower extremities. Arch Med Sci. 2012 May 9;8(2):375-88.
7. Sorci-Thomas MG, Thomas MJ. Why Targeting HDL Should Work as a Therapeutic Tool, but Has Not. J Cardiovasc Pharmacol. 2013 Sep;62(3):239-46.
8. Hennekens CH1, Drowos J.Statins: the high risks of discontinuation and large benefits of continuation. Arch Med Sci. 2011 Dec 31;7(6):931-2.
9. Rizzo M, Battista Rini G. Ezetimibe, cardiovascular risk and atherogenic dyslipidaemia. Arch Med Sci. 2011 Feb;7(1):5-7.
10. Poli G, Biasi F, Leonarduzzi G. Oxysterols in the pathogenesis of major chronic diseases. Redox Biol. 2013 Jan 31;1(1):125-130.
11. Parhofer KG. Update: clinical lipidology. MMW Fortschr Med. 2013 Jul 25;155(13):49-52; quiz 53-4.
12. Sharpe LJ, Brown AJ. Controlling cholesterol synthesis beyond 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR). J Biol Chem. 2013 Jun 28;288(26):18707-15

13. Allian-Sauer MU, Falko JM. New treatments on the horizon for familial hypercholesterolemia. Expert Rev Cardiovasc Ther. 2012 Oct;10(10):1227-37.
14. Tiwari R, Pathak K. Statins therapy: a review on conventional and novel formulation approaches. J Pharm Pharmacol. 2011 Aug;63(8):983-98.
15. Chen GP1, Yao L, Lu X, Li L, Hu SJ. Tissue-specific effects of atorvastatin on 3-hydroxy-3-methylglutarylcoenzyme A reductase expression and activity in spontaneously hypertensive rats. Acta Pharmacol Sin. 2008 Oct;29(10):1181-6.
16. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ. 2003 Jun 28;326(7404):1423-29.
17. Kiss Z, Nagy L, Reiber I, Paragh G, Molnar MP, Rokszin G, Abonyi-Toth Z, Mark L. Persistence with statin therapy in Hungary. Arch Med Sci. 2013 Jun 20;9(3):409-17.
18. Olson EA, Hainsworth DP, Davis G, Hagan JC. Eye on statins: A comprehensive review. Mo Med. 2013 Jul-Aug;110(4):344-8.
19. Huddy K, Dhesi P, Thompson PD. Do the frequencies of adverse events increase, decrease, or stay the same with long-term use of statins? Curr Atheroscler Rep. 2013 Feb;15(2):301-08.
20. Hohenegger M. Drug induced rhabdomyolysis. Curr Opin Pharmacol. 2012 Jun;12(3):335-340.
21. Bruckert E1, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. Cardiovasc Drugs Ther. 2005 Dec; 19(6):403-14.
22. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005 Feb;19(1):117-25.
23. Nezasa K, Higaki K, Matsumura T, Inazawa K, Hasegawa H, Nakano M, Koike M. Liver-specific distribution of rosuvastatin in rats: comparison with pravastatin and simvastatin. Drug Metab Dispos. 2002 Nov;30(11):1158-63.
24. Shirasaka Y, Suzuki K, Nakanishi T, Tamai I. Intestinal absorption of HMG-CoA reductase inhibitor pravastatin mediated by organic anion transporting polypeptide. Pharm Res. 2010 Oct;27(10):2141-9.
25. CAROTENOID PARTICLES AND USES THEREOF. GB Patent Application No. 1101669.8, PCT/GB2012/000075, 25.01.2012.
26. Patel D, Sawant KK. Self micro-emulsifying drug delivery system: formulation development and biopharmaceutical evaluation of lipophilic drugs. Curr Drug Deliv. 2009 Aug;6(4):419-24.
27. Bravo E, Napolitano M. Mechanisms involved in chylomicron remnant lipid uptake by macrophages. Biochem Soc Trans. 2007 Jun;35(Pt 3):459-63.
28. Hoover-Plow J, Huang M. Lipoprotein(a) metabolism: potential sites for therapeutic targets. Metabolism. 2013 Apr;62(4):479-91.
29. Chakravarti R, Sahai V. Compactin -a review. Appl Microbiol Biotechnol. 2004 Jun;64(5):618-24.
30. Roth BD. The discovery and development of atorvastatin, a potent novel hypolipidemic agent. Prog Med Chem. 2002;40:1-22.
31. Ling H, Burns TL, Hilleman DE. Novel strategies for managing dyslipidemia: treatment beyond statins. Postgrad Med. 2012 Nov;124(6):43-54.
32. Banach M1, Mikhailidis DP, Kjeldsen SE, Rysz Time for new indications for statins? J.Med Sci Monit. 2009 Dec;15(12):MS1-5.

Figure 1



Legend

10 patients of both genders aged from 47 to 65 years old with moderate increase in plasma LDL (from 150 to 200 mg/dl) were randomized and enrolled in the pilot clinical trial. Each patient received daily either 20 mg of unmodified Simvastatin or 20 lycosome-formulated statin (Lyco-Simvastatin). Plasma samples were obtained after 30 day treatment and analyzed for lipids. The results are presented in Box-and-Whisker plots versus pre-treatment (baseline) values.

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