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ЛИТЕРАТУРНЫЕ
ОБЗОРЫ

LITERATURE
REVIEWS

STATINS, VASCULAR RISK FACTORS AND STROKE PREVENTION

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ABSTRACT

The most widely prescribed drugs as a first-line therapy for dyslipidemia (DL) are 3-hydroxy-3-methylglutaryl-CoA inhibitors, also known as “statins”. They manifest direct and indirect neuroprotective effects, and also rapid vasoprotection, which occur independently of their cholesterol decreasing activity. Their unique properties have given to statins a place in contemporary therapy guidelines for treatment of the vascular RFs such as DL, arterial hypertension, coronary heart disease (CHD), diabetes mellitus and asymptomatic carotid stenosis in high risk patients. They are recommended for ischemic stroke (IS) primary and secondary prevention and prescribed for long periods. Statin vasoprotective and neuroprotective activities, which manifest immediately after administration, have raised discussion about their beneficial effect in acute IS, and in post-stroke recovery. The withdrawal of statin therapy worsens prognosis and increases mortality rate. There is evidence that oxidative stress and inflammation play role in depression and statin use decreases risk of depressive symptoms in CHD patients. Further well designed randomized studies are needed to investigate the efficacy and safety of statins in acute IS. A challenge for a new study on statins is clarifying whether they possess favorable effects on post-stroke depression in light of the new hypothesis of depression pathogenesis.

Key Words: acute ischemic stroke, primary stroke prevention, post-stroke depression, secondary stroke prevention, statins, vascular risk factors.

The most widely prescribed drugs as a first-line therapy for dyslipidemia (DL) are 3-hydroxy-3-methylglutaryl-CoA inhibitors (HMG-CoA), also known as “statins”. Statins decrease the risk and mortality rate of coronary heart diseases (CHD) and cerebrovascular diseases (CVD). DL is a risk factor (RF) for CHD and CVD, especially for ischemic strokes (IS) (21). Statin dose-dependent therapy decreases plasma total cholesterol and LDL-cholesterol levels. In addition to that the therapy exerts vasoprotective and neuroprotective effects by improving endothelial dysfunction, decreasing oxidative stress and counteracting thrombogenesis in the vascular wall. These effects are due to the direct anti-inflammatory, immunomodulatory, antithrombotic, antioxidant properties and plaque stabilizing effects of statins. (31). These additional statin properties

are of great importance for primary and secondary stroke prevention because of their influence on other vascular RFs such as arterial hypertension (AH), CHD, diabetes mellitus (DM), asymptomatic carotid stenosis (ACS). Some sources state that the use of statins could be beneficial to the treatment of acute IS and subarachnoid hemorrhage (SAH), as well as to the prevention of some depression syndromes.

**LIPID-LOWERING
EFFECTS OF STATINS**

Statins competitively inhibit the enzyme HMG-CoA reductase, which is involved in cholesterol synthesis of the mevalonate metabolic pathway in the liver. Low intracellular cholesterol level increases expression of LDL receptors in hepatocyte membranes, enhances the catabolism of LDL-cholesterol (LDL-C) and reduces its pla-

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sma concentration. As a final result statin dose-dependent therapy leads to a reduction in plasma LDL-C, total cholesterol, triglycerides and a modest increase in HDL-cholesterol (HDL-C). The cholesterol synthesis is most intense at night. Statins with a short plasma half-life should be taken at night for maximum efficiency. Long-acting statins could be taken at any time.

NON-LIPID-LOWERING EFFECTS OF STATINS

The non-lipid-lowering properties of both lipophilic (Atorvastatin, Fluvastatin, Simvastatin) and hydrophilic (Pravastatin, Rosuvastatin) HMG-CoA inhibitors have not been completely clarified yet. Some of them might result from the inhibition of some isoprenoid intermediates in mevalonate pathway of cholesterol synthesis such as geranylpyrophosphate - GGP, farnesylpyrophosphate - FPP and geranylgeranylpyrophosphate (GGPP), which play a key role in modifying a variety of cell signaling proteins of the Ras and Rho GTPase family (31). These proteins regulate a wide spectrum of cellular functions connected to the inflammatory response, including the activation of certain transcription factors, which cause an increase in cytokine production, smooth muscle cell migration, molecules adhesion, an increase in thrombosis and vasoconstriction. Statins increase both endothelial nitric oxide synthase (eNOS) and tissue-type plasminogen activator (tPA) expression, inhibit the expression of plasminogen activator inhibitor, endotelin-1 and cause rapid vasodilatation (31, 34). They reduce angiotensin II-mediated free radical production in vascular smooth muscle cells by a down-regulation of angiotensin AT1 receptor, mRNA expression, vigorously diminish angiotensin II-induced vasoconstriction and cause systolic blood pressure reduction (47). Recent data has shown that statins have certain antihypertensive properties and could be used in an adjunctive antihypertensive therapy (32).

Statins manifest important vasoprotective effects, which have been mediated by their immunomodulatory, anti-inflammatory, antithrombotic properties. Statins possess an abi-

lity to bind directly to lymphocyte cell receptors, to lower the inflammatory cell count in atherosclerotic plaques, to inhibit the monocyte-macrophageal system activity and to reduce MMPs release. They also decrease T lymphocytes' cytotoxicity by activating the anti-inflammatory T-helper system and inhibiting the pro-inflammatory one. As a result, statins reduce the release of pro-inflammatory cytokines, smooth muscle cell proliferation, cell adhesion and migration, cholesterol and fibrin accumulation in the atherosclerotic plaques (34). Thus, the statin therapy is effective in both the early and advanced stage of atherosclerosis.

Statins have shown direct and indirect neuroprotective properties. Direct neuroprotective effects are associated with their ability to inhibit glutamate excitotoxicity by modulating NMDA-receptors (11). Indirect neuroprotective effects are mediated by the mevalonate pathway. Statins modulate the inflammatory process through inhibition of lipoprotein oxidation, reduction in free radical formation and multiple other mechanisms, involving both eNOS and tPA. It has been discovered that statin treatment increases cerebral blood flow in ischemic regions, significantly reduces cerebral infarction volume and neurologic deficits in experimental IS studies (8). Statins induce angiogenesis, neurogenesis, synaptogenesis and brain plasticity after experimental IS (12). This suggests that statin therapy could be useful for cerebral ischemia prevention and better functional recovery after IS.

Statin anti-inflammatory, anti-proliferative and antithrombotic effects occur rapidly after oral administration, much earlier before plasma lipid-lowering (17).

Adverse effects of statins are low. The most common are raised liver enzymes, myalgia, muscle cramps, myopathy, rarely rhabdomyolysis, acute renal failure and liver dysfunction. Other possible adverse effects include non-significantly increased risks for DM and cognitive impairments (13, 40), neuropathy and some gastrointestinal symptoms.

The significance of statin therapy for primary and secondary IS prevention has been documented by several randomized placebo-controlled

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clinical studies. Statins have regularly been recommended along with lifestyle modification by contemporary international guidelines.

PRIMARY IS PREVENTION

RFs for IS and CHD overlap and their aggressive treatment leads to the global decreasing of vascular diseases and their threatening complications (24). Atherosclerosis in different vascular regions (coronary, cerebral or peripheral arteries) has a multifactorial pathogenesis including chronic inflammation, endothelial dysfunction, and lipid accumulation. The atherosclerotic process is relatively reversible because of its dynamic nature. It might progress or regress, depending on the influence of many non-modifiable and modifiable vascular RFs and medical therapy (24, 32, 36). Statins, with their unique properties, have a strong potential to influence and improve the modifiable vascular RFs and to prevent strokes.

The strongest independent and wide-spreading stroke RF in adult populations is AH. The antihypertensive treatment contributes to the reduction of the stroke incidence by 35% to 44% (24). AH occurs rarely in isolation, in less than 20% of the cases, more often in combination with three or more other RFs. Cluster RFs have been detected at four times the rate expected by chance (28) and increase stroke probability (49). The most frequent single RFs in cluster combinations of multiple RFs (three and more than three - MRF) are AH, DL, and obesity (26). There is evidence that they share common metabolic pathways, in which the inflammation and the oxidative stress play an important role (32). RFs should be treated together, not separately. The treatment of only one RF leads to an unacceptably high risk of vascular complications and death, mainly from CHD and stroke in MRF patients. The placebo controlled Anglo-Scandinavian Cardiac Outcome Trial-Lipid Lowering Arm (ASCOT-LLA) has revealed that statin treatment, in combination with the antihypertensive therapy, in AH patients with MRF and normal lipids, significantly reduces both CHD and stroke (41). These results support the thesis for multimodal stroke preventi-

on strategies (24, 26).

CHD is a well-documented modifiable RF for IS (24). Statin treatment of hyperlipidemic patients with CHD (history for and acute myocardial infarction and unstable angina) has resulted in a significant relative risk (RR) reduction of IS and TIA (38, 48).

DM is a well-documented modifiable RF for IS (24). A randomized placebo-controlled trial has observed a significant stroke risk reduction in 5963 high-risk DM patients, who were given statins in addition to their standard therapy. This provides direct evidence that cholesterol-lowering therapy is beneficial to people with DM even if they have not already manifested CHD or DL (14). The comparison between higher-dose and lower-dose statin therapy has pointed out that intensive treatment with a higher dose is more effective and significantly reduces the risk of cerebrovascular events in DM patients with CHD and LDL-C<130 mg/dl and without increasing adverse events (42). In order to lower the risk of a first stroke, it is recommended that DM patients should be under tight blood pressure control and receive statin treatment, especially those with additional RFs (24).

Elevated LDL-C is a well-documented modifiable RF for IS (24) and is significantly associated with the atherothrombotic and lacunar IS subtypes (5). Meta-regression analysis evaluating data from more than 165,000 individuals involved in studies with statin therapy, has shown that the reduction of 1 mmol / L (39 mg /dl) of LDL-C leads to a decrease by 21% of stroke RR (95 % CI 6.3-33.5; P = 0.009) (4). Statin treatment is beneficial to patients with low to normal LDL-C and elevated high-sensitivity C-reactive protein (hs-CRP) and diminishes stroke RR by 48% (P=0.002) (39). It has been recommended for primary IS prevention in reduction of LDL-C in patients with CHD and/or DM, or other RF, in combination with lifestyle changes including healthy hypo-caloric diet, physical activity, and smoking cessation (24). Statin therapy for reducing stroke RR has also been recommended in selected groups of patients with elevated hs-

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CRP, which is a marker of inflammation and has been recognized as a less well-documented modifiable stroke RF (24).

ACS >50% is a well-documented modifiable stroke RF (24). It is often accompanied by CHD, smoking and peripheral arterial disease (36). ACS, which have been detected and followed-up by MRI for 12 - 24 months have shown significant regression, associated with a continuous statin therapy in patients with DL (15). In clinical cases with ACS 30% -70% and lack of surgery indications, a high-dose statin therapy to a target level of LDL-C<70 mg/dL is more effective than a moderate one in achieving carotid plaque stabilization (27). Intensive lipid lowering therapy has significantly reduced the risk of any stroke by 33% in patients with ACS (43). These observations bring to light the strong potency of statins to reverse progression of early and advanced carotid atherosclerosis by restoring endothelial function, remodeling arterial wall and plaque stabilization. There is data that demonstrates the clinical advantage of using statins in patients with moderate ACS for a period of 6.6 ± 2.7 years, during which they were free of ipsilateral stroke (16). Although ACS management is still a matter of debate, for ACS>50% the guidelines recommend aggressive treatment of the other modifiable RFs (AH, CHD, DM, DL, etc.) and a very precise selection of patients for carotid surgery or angioplasty (24). Statin therapy, alone or in combination with other drugs, should be considered in ACS patients (1, 25).

SECONDARY IS PREVENTION

The results of a prospective double-blind placebo-controlled study with high-dose statin therapy have confirmed its efficacy in lowering the risk of recurrent ISs in patients with TIA and IS and without CHD, with a baseline LDL-C between 2.6 and 4.9 mmol/l. They show a significant RR reduction of IS by 18% and a lower 5-year risk of major cardiovascular events (3). Although there have been more brain hemorrhages and elevated liver enzymes, compared with the placebo group,

no statistically significant differences in the overall mortality rate between the two groups have been found (3). Further analysis has revealed that this complication is associated with the male sex, an older age or a prior history of intracerebral hemorrhages (ICH) (22). Intensive statin treatment to a target LDL-C<70 mg/dL level or a reduction of at least 50% in LDL-C should be recommended for reducing the risk of stroke in IS or TIA patients with LDL-C $\geq$ 100 mg/dL, who have evidence of atherosclerosis and who are without known CHD, and also in patients with elevated cholesterol or comorbid CHD (20).

STATINS IN ACUTE STROKES

Statin vasoprotective and neuroprotective activities, which manifest immediately after administration, have raised discussion about their beneficial effect in acute IS and in post-stroke recovery. There is data that patients who have been under statin therapy before and at the moment of IS, and received thrombolytic treatment within 3 hours of the stroke onset, had a significantly improved early neurological deficit, a reduced mortality during hospitalization and a better functional independency at hospital discharge but an increased risk of ICH (2, 6). A trend toward lesser severity of ISs in the statin treatment group of a large placebo-controlled study has also been registered (23). The results from other statin treatment study of acute IS are not so encouraging (35). A significant mortality and dependency increase, an infarction zone enlargement and a delay of the neurological deficits recovery has been observed after withdrawal of a 3-day statin treatment, appointed in the first 24 hours after IS onset or before IS (10). Further well designed randomized placebo-controlled studies are needed to investigate an efficacy and safety of statin treatment in acute IS.

Post-stroke depression (PSD) is the most common mood disorder following a stroke, and also the main factor limiting recovery and rehabilitation and may increase mortality rate. The incidence of PSD is high not only during the first month after the stroke, but even

after several years. Several mechanisms, including neuroinflammation, behavioral and social factors, are involved in its pathogenesis (18). There is growing evidence, which supports the hypothesis that inflammation with elevated proinflammatory cytokines, oxidative stress, immune mechanisms with activated both humoral and cell-mediated pathways, impaired neuroplasticity and progressed neurodegeneration play a role in the depression pathogenesis (9, 19). A prospective 6 years cohort study has found that statin use was associated with a 38% decreased risk of subsequent depressive symptoms in patients with CHD (OR, 0.62; 95% CI, 0.41-0.95; P = .02) (37). Similar results, revealing statins preventive effects on the development of depression, have been reported in another study. Angioplasty, myocardial infarction, or coronary artery bypass graft surgery patients were included in it and were followed up prospectively for 9 months to assess whether a relationship between a decreased risk of depression and statin therapy exists. This study also shows evidence which supports the hypothesis of the role of oxidative and inflammatory processes in depression (44). So far there is no published clinical data on the matter of statins' positive effect on PSD. This may be a new challenge for future research.

It is assumed that the relationship between ICH and elevated cholesterol is reciprocal (7). There is controversial data about statin use prior to ICH, which might be either associated with reduced mortality and neurological disability, with a higher chance for good outcome (30) or not (29).

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Statin treated patients after SAH in small, randomized, controlled clinical trials have shown reduced vasospasm, delayed ischemic deficits and an improved cerebral autoregulation (33, 45). A meta-analysis, which has assessed the efficacy of statin treatment in SAH patients, does not support their usage despite the findings of beneficial effects because of a lack of a statistical significance of the results and very small sample sizes of the studies (46). New well-designed studies evaluating the effectiveness of statins in preventing vasospasms and delayed ischemic deficits in SAH are needed.

CONCLUSION

Statins manifest rapid vasoprotective effects which occur independently of their cholesterol decreasing activity. The lipid-lowering, vasoprotective and neuriprotective properties have given statins an important place in contemporary therapy guidelines for treatment of the most important vascular RFs such as DL, AH, CHD, DM and ACS in high risk patients. They are recommended for IS primary and secondary prevention and prescribed for long periods of time with commonly rare and mild side effects. The withdrawal of statin therapy is associated with a worse prognosis and increased mortality in TIA and IS patients. Further studies assessing statins' effects in acute IS are needed. A challenge for a new study on statins is clarifying their ability to prevent PSD, based on their antiinflammatory, antioxidant and immunomodulatory activities in light of the new hypothesis of depression pathogenesis.

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РЕЗЮМЕ

СТАТИНЫ, СОСУДИСТЫЕ ФАКТОРЫ РИСКА И ПРОФИЛАКТИКА ИНСУЛЬТА

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Наиболее широко используемые лекарства для терапии первой линии при дислипидемии (ДЛ) являются ингибиторы 3-гидрокси-3-метилглутарил КоА, также известные как "статины". Они проявляют прямые и косвенные нейропротективные и также быстрые вазопротективные эффекты, которые происходят независимо от их влияния на уменьшения холестерина. Их уникальные свойства дали статинам место в современных рекомендациях по терапии сосудистых факторов риска, таких как, ДЛ, артериальная гипертензия, ишемическая болезнь сердца (ИБС), сахарный диабет и бессимптомный каротидный стеноз у пациентов высокого риска. Они рекомендованы для первичной и вторичной профилактики ишемического инсульта (ИИ) и предписаны в течение многих длительных периодов. Вазопротективные и нейропротективные действия статинов, которые немедленно проявляют себя после применения, подняли дискуссию об их благоприятном воздействии в остром, и в восстановительном периоде инсульта. Отказ в лечении статином ухудшает прогноз и увеличивает смертность. Есть доказательства, что оксидативный стресс и воспаление играют роль в депрессии и статины уменьшают депрессивных признаков у пациентов с ИБС. Необходимы хорошо разработанные рандомизированные исследования, для доказательств эффективности и безопасности статинов в остром периоде ИИ. Испытание для нового исследования статинов разъяснит, обладают ли они благоприятными эффектами на депрессию после инсульта с точки зрения новой гипотезы патогенеза депрессии.

Ключевые слова: острый ишемический инсульт, первичная профилактика инсульта, депрессия после инсульта, вторичная профилактика инсульта, статины, сосудистые факторы риска.

XÜLASƏ

STATİNLƏR, VASKULYAR RİSK AMİLLƏRİ VƏ İNSULTLARIN PROFİLAKTİKASI

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Dislipidemiyalar (DL) zamanı ən geniş istifadə edilən ilk seçim preparatları "statinlər" kimi tanınan 3-hidroksi-3-metilqlutaril KoA-nın inhibitorlarıdır. Onlar xolesterinin səviyyəsinin azalmasına təsirlərindən asılı olmayaraq birbaşa və dolayı neyroprotektiv və sürətli vazoprotektiv təsir göstərirlər. Statinlərin unikal xüsusiyyətləri onlara DL, arterial hipertenziya, ürəyin işemik xəstəliyi (ÜİX), şəkərli diabet və asimptomatik karotid stenoza kimi vaskulyar risk amillərinin müalicə üzrə müasir kliniki protokollarda yer almasına təsir etmişdir. Onlar işemik insultların

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(İİ) birincili və ikincili profilaktikasında tövsiyə edilir və uzun müddətdir ki, təyin edilir. Statinlərin təyin ediləndən dərhal sonra özünü göstərən vazoprotektiv və neyroprotektiv effektləri insultların kəskin və bərpa dövrlərində onların müsbət təsiri barədə müzakirələrə səbəb olmuşdur. Statinlərlə müalicədən imtina xəstəliyin proqnozunu pisləşdirir və ölümü artırır. Oksidativ stress və iltihabın depressiyanın yaranmasında rolu və statinlərin ÜİX olanlarda depressiyanın əlamətlərini azaltması barədə sübutlar vardır. İİ zamanı kəskin dövrdə statinlərin effektivliyini və təhlükəsizliyini yoxlamaq üçün Yüksək səviyyədə təşkil edilmiş randomizə olunmuş tədqiqatlara ehtiyac duyulur. Digər tədqiqatlar depressiyanın patogenezinin yeni hipotezi nöqtəyi nəzərdən statinlərin insultdan sonra depressiyaya müsbət təsirinin olmasını araşdıracaq.

Açar sözlər: kəskin işemik insult, insultların birincili profilaktikası, insultdan sonrakı depressiya, insultların ikincili profilaktikası, statinlər, vaskulyar risk amilləri.

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