Odustajemo li prelako od adekvatnih doza statina?

Are we giving up on adequate statin doses too easily?

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SAŽETAK: Koronarna bolest srca vodeći je uzrok mortaliteta u razvijenim zemljama, a hiperkolesterolemija jedan je od značajnih čimbenika rizika za razvoj ateroskleroze. U nastojanjima reduciranja učestalosti neželjenih kardiovaskularnih događaja, nužnost je efikasno sniziti koncentraciju serumskog LDL kolesterola, posebice stoga što je to čimbenik rizika koji, uz terapiju, možemo znatno modificirati. Statini su temeljni lijekovi za primarnu i sekundarnu prevenciju kardiovaskularnih bolesti, a njihovo djelovanje dovodi do sniženja ukupnog i LDL kolesterola u plazmi, ali usporivanju procesa ateroskleroze i stabilizaciji ateroma pridonose i brojni drugi učinci statina, povrh samo sniženja razine kolesterola. Upravo iz metaboličkog učinka statina razjašnjena je i moguća etiologija miopatije koja se pojavljuje kao relativno česta pritužba bolesnika, zbog čega se smanjuje doza lijeka ili prekida liječenje, čime se bolesnik izlaže ponovno povišenom riziku za razvoj neželjenoga kardiovaskularnog događaja. Stoga su ovdje navedene i dosadašnje spoznaje o etiologiji i liječenju spomenute nuspojave.

SUMMARY: Coronary heart disease is the leading cause of mortality in developed countries, and hypercholesterolemia is one of the significant risk factors for the development of atherosclerosis. Attempts to reduce the incidence of cardiovascular events necessitate efficient lowering of LDL cholesterol concentrations, especially since this is a risk factor that we can significantly modify through treatment. Statins are basic drugs for the primary and secondary prevention of cardiovascular diseases, and their activity leads to a reduction in plasma levels of total and LDL cholesterol, but other numerous effects of statins beyond just the reduction of cholesterol levels contribute to atheroma stabilization and slowing down the process of atherosclerosis. It is the metabolic effect of statins that explains the possible etiology of myopathy, which is a relatively common patient complaint leading to reduction in dosage or treatment termination, which once again exposes the patient to increased risk of the development of unwanted cardiovascular events. Thus, the current knowledge on the etiology and treatment of this side effect is also addressed in this article.

KLJUČNE RIJEČI: statini, pleiotropni učinak, prevencija kardiovaskularnih bolesti, miopatije.

KEYWORDS: statins, pleiotropic effect, prevention of cardiovascular diseases, myopathies.

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Uvod

Već dugo statine ne smatramo "samo" lijekovima za redukciju serumskih vrijednosti kolesterola, neovisno o tome razmišljamo li o primarnoj, a posebice ne ako govorimo o sekundarnoj prevenciji kardiovaskularnih bolesti. Statinski učinak na smanjenje rizika najjednostavnije pratimo mjerenjem koncentracije serumskog kolesterola, ali je ukupni pad kardiovaskularnog rizika rezultat njegova metaboličkog učinka koji postiže inhibicijom 3-hidroksi-metilglutaril-CoA (HMG-CoA) reduktaze, enzima koji se nalazi u mnogim

Introduction

Statins have not been considered "just" drugs for the reduction of serum cholesterol for a long time, regardless of whether we are talking about primary or especially secondary prevention of cardiovascular diseases. The effect of statins on risk reduction is most easily determined by measuring serum cholesterol concentrations, but the total cardiovascular risk reduction is the effect of their metabolic effect that is the result of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme found in

tkivama: jetri, stanicama endotela, upalnim i drugim stanicama. Enzim HMG-CoA uključen je u prvi korak važnoga metaboličkog mevalonatnog puta koji opskrbljuje stanice bioaktivnim spojevima koji su presudni za mnogobrojne stanične procese. Konačni produkti mevalonatnog puta uključuju sterolne izoprenoide (poput kolesterola) i nesterolne izoprenoide, poput dolikola, hem-A, isopentil RNA i ubikinona[1]. Inhibiranje mevalonatnog puta i posljedičnoga smanjenja proizvodnje izoprenoida, odgovorno je za antioksidativne, antiinflamatorne i antiaterosklerotske učinke statina koje nazivamo pleiotropnim učincima. Čini se da je upravo učinak statina na hepatocite odgovoran za opisane učinke. Istraživanja su, nadalje, pokazala da smanjenjem koncentracije izoprenoida dolazi do posttranslacijske modifikacije unutrastaničnih, signalizacijskih proteina, čime se reguliraju važni proliferacijski i oksidativni procesi aterogeneze[2,3]. Svjesnost postojanja pleiotropnih učinaka nastupila je nakon niza studija kojima je dokazano da unatoč jednakom učinku na serumske lipide, primjenu statina neobjašnjivo prati mnogo brže smanjenje kardiovaskularnog rizika u odnosu prema upotrebi niacina, fibrata ili ezetimiba[4]. Primjena atorvastatina dovodi do poboljšanja endotelne funkcije u pušača unutar samo 48 sati, a još nije nastupila znatna promjena koncentracije serumskih lipida. Endotelna se disfunkcija uz statinsku terapiju oporavlja zahvaljujući pojačavanju učinka dušičnog oksida i endotelnih progenitornih stanica, a smanjenju učinka ciklooksigenaze 2 i endotelina 1. Rosuvastatin u dozi od 20 mg, prema studiji JUPITER, u primarnoj prevenciji dovodi do znatnog smanjenja rizika od infarkta miokarda i moždanog udara, iako su inicijalne vrijednosti LDL kolesterola u studijskoj populaciji iznosile < 3,4 mmol/L, ali uz povišene znakove upalnog odgovora s prosječnom vrijednosti hs-CTP-a>2 mg/L, tako da se protektivno djelovanje rosuvastatina više veže za smanjenje protuupalnog učinaka od *per se* sniženja vrijednosti LDL kolesterola[5]. Opisano protuupalno djelovanje posljedica je statinskoga smanjenja učinka CRP-a, CD40, adhezijskih molekula i proupalnih citokina. Treći segment pleiotropnih svojstava statina proizlazi iz smanjenja trombogeneze smanjenjem učinaka fibrinogena i smanjenjem agregacije trombocita uz redukciju učinka tromboksana A2 i inhibitora aktivatora plazminogena (PAI) 1, a povećanjem učinka aktivatora tkivnoga plazminogena (tPA)[6]. Dodatnu sigurnost u primjeni atrovastatina i rosuvastaina u visokim dozama daju studije koje su uz intravaskularni ultrazvuk dokazale regresiju ateroskleroze (ASTEROID, COSMOS, REVERSAL). Navedeni podatak daje dozu optimizma, posebice za intrakoronarne lezije koje nisu pogodne za perkutanu intervenciju ni za kardiokirurišku revaskularizaciju.

Demistifikacija mijalgije

Međutim, čini se da upravo zbog interferiranja s mevalonatnim putem dolazi do razvoja jedne od najčešćih (10 – 11 %) nuspojava i razloga odustajanja od statinske terapije. Riječ je o mijalgiji koja se klinički prezentira bolovima u mišićima i slabošću pojedinih mišićnih skupina[7]. Ako uz kliničku sliku miopatije nalazimo i deseterostruki porast aktivnosti enzima kreatinin-kinaze, tada je riječ o mionekrozi, a najteži oblik mionekroze jest rabdomioliza koju definira pojava mi-

many tissues: the liver, endothelial cells, inflammatory cells, and others. The HMG-CoA enzyme is involved in the first step of the important metabolic mevalonate pathway that supplies cell with bioactive compounds which are crucial for many cellular processes. The final products of the mevalonate pathway include sterol isoprenoids (such as cholesterol) and non-sterol isoprenoids, such as dolichol, hydroxyethyl methacrylate (HEMA), isopentyl RNA, and ubiquinone[1]. Inhibition of the mevalonate pathway and the consequent reduction in the production of isoprenoids is responsible for the antioxidative, anti-inflammatory, and anti-atherosclerotic effects of statins, which we call pleiotropic effects. It seems that it is the effect of statins on hepatocytes that is responsible for these effects. Furthermore, studies have shown that reduction in the concentration of isoprenoids leads to posttranslational modification of intercellular signalization proteins, which regulates important proliferative and oxidative atherogenic processes[2,3]. Awareness of the existence of these pleiotropic effects is a result of a number of studies demonstrating that, despite an equal effect on serum lipid levels, statin administration is associated with an inexplicable and significantly faster reduction in cardiovascular risk in comparison with the use of niacin, fibrates, or ezetimibe[4]. The application of atorvastatin leads to improvement of endothelial function in smokers within just 48 hours, before there has been a significant change in serum lipid concentrations. Under statin treatment, endothelial dysfunction is also improved due the strengthening of the effect of nitric oxide and endothelial progenitor cells and a reduction of the effects of cyclooxygenase 2 and endothelin 1. Based on the JUPITER study, rosuvastatin in a dose of 20 mg in primary prevention leads to significant reduction of myocardial infarction risk and risk of stroke, despite the fact that the initial LDL cholesterol values in the study population were <3.4 mmol/L, but with increased signs of inflammatory response with average hs-CTP values >2 mg/L, so the protective effect of Rosuvastatin is tied more to reduction of anti-inflammatory effects than LDL cholesterol reduction *per se*[5]. This anti-inflammatory effect is a consequence of the reduced effects of CRP, CD40, adhesion molecules, and anti-inflammatory cytokines caused by statins. The third segment of the pleiotropic characteristics of statins is a result of thrombogenesis reduction due to a reduction in the effects of fibrinogen and platelet aggregation with a reduction of the effects of thromboxane A2 and plasminogen activator inhibitors (PAI) 1, and an increase in the effects of tissue plasminogen activators (tPA)[6]. Added assurance for the application of atorvastatin and rosuvastatin at high doses has been given by studies that have used intravascular ultrasound to demonstrate atherosclerosis regression (ASTEROID, COSMOS, REVERSAL). This fact is cause for a measure of optimism, especially regarding intracoronary lesions that are unsuitable for both percutaneous intervention and surgical revascularization.

Demystification of myalgia

However, it seems it is this interference with the mevalonate pathway that causes the development of one of the most common (10-11%) side effects and reasons for termination of

oglobinurije uz mogući razvoj akutnoga bubrežnog zatajenja. Ubikinon, koji je poznatiji pod nazivom koenzim Q10 (CoQ10), nalazi se u staničnoj membrani mitohondrija, u svim stanicama, a osnovna mu je funkcija prijenos elektrona s NADH dehidrogenaze i sukcinatdehidrogenaze na citokrom, čime omogućuje proizvodnju ATP-a, osnovnog izvora energije svake stanice. Statini reduciraju koncentraciju CoQ10, a, budući da je za funkciju poprečnoprugaste muskulature potrebna velika količina energije, smatralo se da je nedostatak koenzima Q10 moguće objašnjenje etiologije mijalgije. Incijalno su klinčke studije pokazale dobrobit od suplementacije koenzima Q10, ne samo zbog smanjenje mijalgije, nego i zbog njegova učinka na smanjenje oksidacije LDL kolesterola. Međutim, rizični su čimbenici za nastanak mijalgije na statinskoj terapiji višestruki: ovise su o dozi lijeka, interakciji s drugim lijekovima, asteničnoj građi, operacijama, dobi, fizičkoj aktivnosti, infekcijama, bubrežnoj insuficijenciji, oštećenju jetre, ženskom spolu, hipertrigliceridemiji, arterijskoj hipertenziji, šećernoj bolesti, hipotireozi, nasljednim bolestima mišića, hiperkalijemiji te o genetskim mutacijama s disfunkcijom mitohondrija[8]. Iz navedenog je jasno zašto dodatak koenzima Q10 kod "statinske mijalgije" djeluje u samo nekih bolesnika[9]. Danas ne postoje preporuke za rutinsku upotrebu koenzima Q10 uz terapiju statinom, iako se većina autora slaže da je njihova upotreba razumna ako bolesnik pati od mijalgije, posebice što se za sada ne nalazi mogući štetni učinak koenzima Q10. Također se preporučuje istražiti moguću interakciju lijekova, posebice onih lijekova koji inhibiraju crijevne i jetrene CYP enzime. Iz navedenog je očito da smanjenje doze ili prekid terapije statinom, bez obzira na eventualnu pojavu mijalgije, nije opravdan jer se time znatno povećava kardiovaskularni rizik, kao i rizik od velikih, neželjenih događaja.

Pleiotropni učinici statina u akutnome koronarnom incidentu

Dobro su poznati različiti patološki mehanizmi koji su uključeni u razvoj akutnoga koronarnog sindroma, od endotelne disfunkcije, aktivacije upalne i prokoagulantne kaskade, što objašnjava rupturiranje plaka i intrakoronarno stvaranje tromba s posljedičnom djelomičnom ili potpunom okuzijom arterije. Statini blokiraju sva tri navedena mehanizma. Od 2004. godine dobro je poznato da nakon akutnoga koronarnog sindroma, po postizanju stabilnosti bolesnika, posebice nakon učinjene perkutane koronarne intervencije, postoji značajna dobrobit od intenzivnog sniženja serumskih lipida atrovastatinom u usporedbi s umjerenim sniženjem pravastatinom[10]. Navedeni su rezultati potaknuli istraživače da ispitaju sigurnost i učinkovitost statina u izravnom liječenju akutnoga koronarnog sindroma kao prve linije terapije u nestabilnog bolesnika. Takav terapijski pristup ohrabrile su brojne eksperimentalne studije koje su ispitivale učinkovitost statina u stanjima akutne ishemije i čini se, prema dostupnim podatcima, da se može očekivati niži postotak periproceduralnog infarkta tijekom koronarne intervencije i niža incidencija novih kardiovaskularnih događaja[11], ali i sniženje nastanka nove nestabilne angine četiri mjeseca nakon akutnoga koronarnog zbivanja.

statin treatment. This side effect is myalgia, which clinically presents with muscle pain and weakness in certain muscle goups[7]. If the clinical picture of myopathy is accompanied by a tenfold increase in the activity of the creatine kinase enzyme, we are dealing with myonecrosis; the most severe form of myonecrosis is rhabdomyolysis, which is defined by myoglobinuria with the possible development of acute renal failure. Ubiquinone, better known under the name coenzyme Q10 (CoQ10), is found in the cell membranes of mitochondria in all cells, and its basic function is electron transfer from NADH dehydrogenase and succinate dehydrogenase to cytochromes, allowing production of ATP, the basic energy source in every cell. Statins reduce CoQ10 concentrations, and since a large amount of energy is necessary for skeletal muscle function it was believed that the lack of coenzyme Q10 could explain the etiology of myalgia. Initially, clinical studies found that coenzyme Q10 supplementation was beneficial, not only for myalgia reduction but also for its effect on the reduction of LDL cholesterol oxidation. However, there are multiple risk factors for myalgia in statin treatment: they are dependent on drug dosage, interaction with other medication, asthenic constitution, surgeries, age, physical activity, infection, renal insufficiency, liver damage, female sex, hypertriglyceridemia, arterial hypertension, diabetes, hypothyreosis, congenital muscle diseases, hyperkalemia, and genetic mutations with mitochondrial dysfunction[8]. This explains why coenzyme Q10 supplements for "statin allergy" work only in some patients[9]. There are currently no recommendations for routine use of coenzyme Q10 with statin therapy, although most authors agree that their use is reasonable if the patient suffers from myalgia, especially since no possible harmful effects of coenzyme Q10 have been found so far. Exploring possible drug interaction is also recommended, especially for those drugs that inhibit intestinal and liver CYP enzymes. It is clear that dose reduction or treatment termination for statins is not justified regardless of the eventual manifestation of myalgia, since that significantly increases cardiovascular risk and risk of severe adverse events.

Pleiotropic effects of statins in acute coronary incidents

The different pathological mechanisms involved in the development of acute coronary syndrome are well known, including endothelial dysfunction and activation of inflammatory and procoagulant cascades, which explain plaque rupture and intracoronary thrombus formation with consequent partial or complete arterial occlusion. Statins block all three of these mechanisms. It has been known since 2004 that after patient stabilization has been achieved after acute coronary syndrome, especially following percutaneous coronary intervention, there is significant benefit to intensive reduction of serum lipid levels using atorvastatin in comparison with a moderate reduction with pravastatin[10]. These results encouraged researchers to examine the safety and effectiveness of statins in direct treatment of acute coronary syndrome as the first line of treatment in unstable patients. This approach was encouraged by numerous experimental studies assessing the effectiveness of statins in acute ischemic states, and the

Zaključak

Brojne studije s uključenim velikim brojem bolesnika, s primjenjenim visokim dozama statina, tijekom dugog niza godina, svrstavaju statine u sigurne lijekove s opetovnim dokazima o znatnom smanjenju pobola i smrtnosti, neovisno o tome je li riječ o primarnoj ili sekundarnoj prevenciji, ali i dalje se često pribjegava nižim dozama lijeka kojima se ne postižu ciljne vrijednosti kolesterola prema smjernicama, a poznato je da su i pleiotropni učinci lijeka vezani za dozu statina. Stoga bolesnike s akutnim koronarnim sindromom i visokorizične bolesnike sa stabilnim kroničnim oblicima ateroskleroze treba nastaviti liječiti visokim dozama statina. Nažalost, povremeno se terapija statinom i bezrazložno prekida. Statini su dokazali svoju snagu i učinkovitost uz vrlo rijetke ozbiljne nuspojave pa stoga njihovu moć treba optimalno iskoristiti u redukciji pobola i pomora od kardiovaskularnih incidenata u sve starijoj populaciji. Naravno, opet je potrebno naglasiti da je za optimalnu prevenciju i liječenje ateroskleroze prijeko potrebna dobra regulacija svih čimbenika rizika, ali je i nužna promjena životnoga stila, za što odgovornost snosi sam bolesnik.

available data indicate that we can expect a lower incidence of periprocedural infarction during coronary intervention as well as lower incidence of new cardiovascular events[11], but also a reduction in the appearance of new unstable angina four months after acute coronary events.

Conclusion

Numerous studies with large numbers of patients that received high statin doses over a period of many years have placed statins in the group of safe drugs that have been repeatedly demonstrated to significantly reduce morbidity and mortality both in primary and secondary prevention, but physicians still often resort to lower doses that do not achieve target cholesterol values according to guidelines; it is also known that the pleiotropic effects of statins are dose-related. Thus, patients with acute coronary syndrome and high-risk patients with stable chronic atherosclerotic disease should still be treated with high statin doses. Unfortunately, statin treatment is sometimes terminated for no good reason. Statins have proven their power and effectiveness while having very rare side effects, so their strengths should be optimally applied for the reduction of morbidity and mortality from cardiovascular incidents in the aging population. Of course, it should once again be pointed out that optimal prevention and treatment of atherosclerosis requires not only good regulation of all risk factors, but also lifestyle changes for which the patients themselves are responsible.

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