Klinički dokazi djelotvornosti Krkinog rosuvastatina u liječenju hiperlipidemije, s fokusom na dodatnim jačinama doza

Clinical Evidence of the Efficacy of Krka's Rosuvastatin in the Treatment of Hyperlipidemia with Focus on Additional Dosage Strengths

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SAŽETAK: Dislipidemija je povezana s najvećim rizikom za srčano-žilne bolesti u populaciji. Od raznih preventivnih postupaka, dokazi iz randomiziranih kontroliranih studija podržavaju važnost agresivnog smanjenja vrijednosti lipida koje se najsnažnije postiže uporabom statina. Kliničke studije su pokazale da čak i malo smanjenje LDL kolesterola ima važan klinički učinak. No, usprkos jasnim dokazima korisnosti terapije statinima, ti lijekovi se i dalje nedovoljno koriste ili se primjenjuju u nedostatnim dozama. Većina pacijenata s dislipidemijom liječi se najnižim dozama, a liječnici vrlo rijetko propisuju najviše doze. Da bi se potpomoglo zatvaranje tog terapijskog jaza, Krka je priredila širok spektar jačina rosuvastatina, uključujući dvije doze srednje jačine od 15 mg i 30 mg. Te jačine omogućuju individualnu prilagodbu liječenja te postizanje željene razine lipida u većeg broja pacijenata.

SUMMARY: Dyslipidemia is associated with the highest population attributable risk for cardiovascular disease. Of various cardiovascular preventive therapies, the evidence from randomised controlled studies supporting the importance of aggressive lipid lowering is the most robust for statins. Clinical studies have shown that even a small reduction of LDL cholesterol has an important clinical effect. However, despite clear evidence of the benefits of statin therapy, these drugs are still underused or underdosed. The majority of patients with dyslipidemia are treated with the lowest doses, and doctors use the highest doses only very rarely. To help close the therapeutic gap, Krka has made available a wide range of rosuvastatin dosage strengths, including two intermediate strengths of 15 mg and 30 mg. These enable treatment to be individually adjusted and result in more patients reaching target lipid levels.

KLJUČNE RIJEČI: rosuvastatin, jačine doza, LDL kolesterol, kardiovaskularna bolest.

KEYWORDS: rosuvastatin, dosage strengths, LDL cholesterol, cardiovascular disease.

CITATION: Cardiol Croat. 2014;9(7-8):320-323.

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RECEIVED:
July 10, 2014
ACCEPTED:
July 18, 2014

Dislipidemija je jedan od najvažnijih rizičnih čimbenika za srčano-žilne bolesti (CVD) i važan je čimbenik u njihovoj prevenciji, dok je LDL kolesterol (LDL-C) glavni cilj liječenja dislipidemija. Među raznim postupcima prevencije kardiovaskularnih bolesti, dokazi iz randomiziranih kontroliranih studija podržavaju važnost agresivnog smanjenja lipida koje se najsnažnije postiže primjenom terapije statinima. Kliničke su studije pokazale da čak i mala redukcija vrijednosti LDL-C ima klinički učinak.

Dyslipidemia is one of the most important risk factors for cardiovascular disease (CVD) and an important priority in its prevention, while low-density lipoprotein cholesterol (LDL-C) represents the main target of dyslipidemic therapy. Of various CV preventive therapies, the evidence from randomized controlled studies supporting the importance of aggressive lipid lowering is the most robust, particularly for statin therapy. Clinical studies have shown that even a small reduction of LDL-C has

Za svaki 1% redukcije vrijednosti LDL-C, smanjuje se relativni rizik za veliki koronarni događaj za 1%.

Rosuvastatin, kao jedan od najsnažnijih statina, učinkovito smanjuje LDL-C, totalni kolesterol (TC) i trigliceride (TG) te povećava vrijednost HDL kolesterola (HDL-C) u predvidljivom omjeru, ovisno o dozama. Uz njegovu učinkovitost u moduliranju lipida, rosuvastatin pokazuje i dodatna djelovanja, često nazivana pleiotropnima, koji dovode do značajnih kliničkih učinaka. Značajan broj eksperimentalnih i kliničkih studija pokazao je pozitivne učinke rosuvastatina na funkciju endotela, na oksidizirani lipoprotein male gustoće, na upalu, stabilnost plaka, vaskularno preoblikovanje, na hemostazu, srčani mišić i na komponente živčanog sustava.

Statini su tradicionalno dostupni u četiri dozne veličine, od 10 mg, 20 mg, 40 mg i 80 mg, no rosuvastatin je iznimka jer je dostupan i u jačinama doza od 5 mg do 40 mg. Činjenica da se većina pacijenata liječi s pomoću dvije najmanje doze i da liječnici rijetko propisuju najveće doze statina, pokazuje da postoji potreba za većim izborom doza srednje jačine. Tablete rosuvastatina od 15 mg i 30 mg su dvije nove jačine koje je Krka prva uvela da bi pomogla optimalnu i učinkovitu hipolipidemijsku terapiju (koja se mjeri smanjenjem LDL-C, TG, TC te povećanjem HDL-C) i da pospješi zaštitu srčano-žilnog sustava kroz molekularno specifične pleiotropne učinke. Širok raspon jačina rosuvastatina omogućuje prilagođavanje liječenja prema individulanim potrebama svakog bolesnika te u konačnici povećava vjerojatnost dostizanja ciljnih razina lipida.

Kao što je prikazano u objavljenim kliničkim studijama i meta-analizama, klinički učinci rosuvastatina jačine doza od 15 mg i 30 mg su predvidljivi unutar raspona doza koje su dosad bile odobrene i uspostavljene na tržištu. K tomu, obećavajući podatci prikupljeni su tijekom dvije post-autorizacijske studije, koje su provedene u Sloveniji i Slovačkoj, a koje su

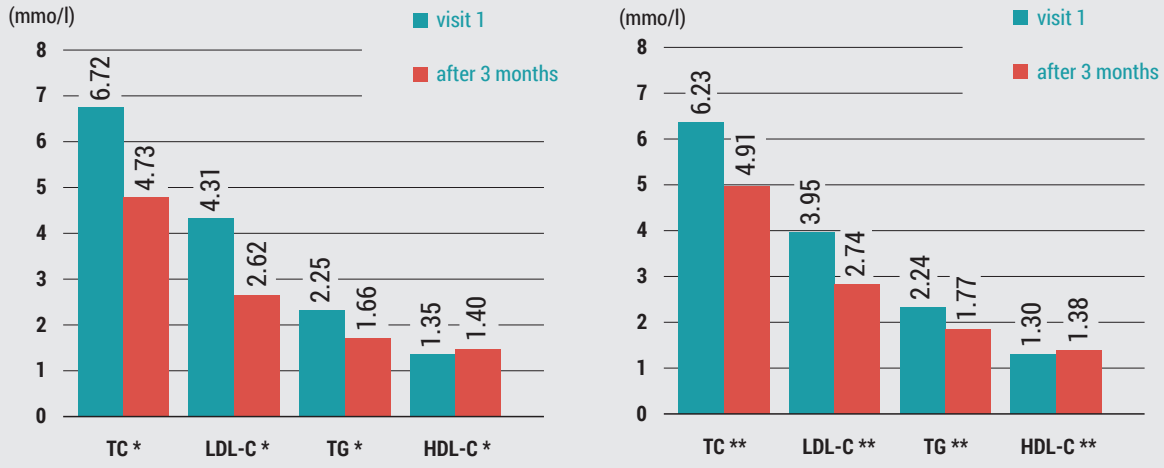
a clinical effect. Every 1% reduction in LDL-C levels reduces the relative risk for major coronary heart disease events by approximately 1%.

Rosuvastatin, as one of the most potent statins, effectively reduces LDL-C, total cholesterol (TC) and triglycerides (TG) and increases high-density lipoprotein cholesterol (HDL-C) in a predictable dose-dependent manner. Moreover, apart from its beneficial lipid-modulating effects rosuvastatin exerts several extra effects, often called pleiotropic, which result in meaningful clinical benefits. A substantial number of experimental and clinical studies have demonstrated favourable effects of rosuvastatin on endothelial function, oxidised low-density lipoprotein, inflammation, plaque stability, vascular remodelling, hemostasis, cardiac muscle, and components of the nervous system.

Statins were traditionally available in four dosage strengths, mostly 10 mg, 20 mg, 40 mg and 80 mg, with the exception of rosuvastatin, which is available in dosage strengths from 5 mg to 40 mg. The fact that a majority of patients are treated with the two lowest doses and that physicians rarely prescribe the highest doses of statins indicates there is a need for more intermediate dosage strengths. Tablets of 15 mg and 30 mg of rosuvastatin are two new dosage strengths of rosuvastatin, first introduced by Krka to facilitate optimal and effective hypolipidemic therapy (measured by decrease in LDL-C, TG, and TC and increase in HDL-C) and improve CV protection through molecule-specific pleiotropic effects. The wide range of rosuvastatin dosage strengths enables treatment adjustment to the requirements of individual patients and ultimately increases the likelihood of reaching the target lipid levels.

As demonstrated in published clinical studies and meta-analyses, the clinical effect of rosuvastatin 15 mg and 30 mg dosage strengths is predictable within the range of doses already approved and established on the market. Furthermore, promising data have been obtained from two post-authorisa-

FIGURE 1.



Clinical effect (mean values during treatment) of Krka's rosuvastatin in the Slovenian study (left) and in the Slovakian study (right). *p < 0.0001, **p < 0.01

proučavale učinkovitost i sigurnost titrirajućih Krkinih doza rosuvastatina u liječenju hiperlipidemije. Cilj je tih studija procjena ne samo cjelokupnog učinka i sigurnosti Krkinog rosuvastatina već i učinkovitosti i sigurnosti individualnih doza, uključujući uporabu doza jačine 15 mg i 30 mg, pri normalnoj kliničkoj praksi.

U studiji je sudjelovalo 6.366 pacijenata iz Slovenije i 512 pacijenata iz Slovačke. U obje države nadzor pacijenata je trajao 3 mjeseca. Studije su uključivale pacijente s hiperlipidemijom obaju spolova, u dobi iznad 18 godina, s primarnom hiperkolesterolemijom ili miješanom dislipidemijom (tip IIb) ili homozigotnom familijarnom hiperkolesterolemijom, u kojih je odgovor na dijetu i druge nefarmakološke mjere bio nedostatan.

Obje su studije pokazale da je titriranje doze Krkinog rosuvastatina, uključujući uporabu jačina od 15 mg i 30 mg, bilo učinkovito i sigurno pri liječenju hiperlipidemije. TC, LDL-C i TG su se statistički značajno smanjili, a HDL-C se povećao na kraju studije. Rezultati su bili slični u slovenskoj i slovačkoj studiji (**slika 1**):

- U slovenskoj studiji, gdje je srednja doza bila 17,3 mg, prosječna smanjenja su bila: TC za 29,6%, LDL-C za 39,2%, TG za 26%, dok je HDL-C povećan za 3,7%.
- U slovačkoj studiji, gdje je srednja doza bila 19,3 mg, prosječna smanjenja su bila: TC za 21,2%, LDL-C za 30,6%, TG za 21%, dok je HDL-C povećan za 6,2%.

Linearna povezanost između doze i smanjenja LDL- C je bila očita (**slika 2**).

U obje studije (**slika 3**), ukupni rezultat liječenja Krkinim rosuvastatinom procijenjen je kao vrlo uspješan ako je ciljna razina LDL-C dostignuta (LDL-C ≤ 2,99 mmol/L u primarnoj prevenciji ili LDL-C ≤ 2,49 mmol/L u sekundarnoj prevenciji), kao uspješan ako je razina LDL-C smanjena za više od 10%, ali ciljna razina nije dostignuta, i kao neuspješan ako je vrijed-

tion studies, conducted in Slovenia and in Slovakia, on the efficacy and safety of titrating Krka's rosuvastatin dose in hyperlipidemia treatment. The aim of these studies was to evaluate not only the overall efficacy and safety of Krka's rosuvastatin but also the efficacy and safety of individual doses, including the use of the 15 mg and 30 mg dosage strengths, in normal clinical practice.

A population of 6.366 patients from Slovenia and 512 patients from Slovakia participated in the studies. In both countries, the monitoring of individual patients lasted for 3 months. The studies included hyperlipidemic patients of both sexes, aged over 18 years, with primary hypercholesterolemia or mixed dyslipidemia (type IIb) or homozygous familial hypercholesterolemia, in whom the response to diet and other non-pharmacological measures had been inadequate.

Both studies demonstrated that up-titrating Krka's rosuvastatin dose, including the use of the 15 mg and 30 mg dosage strength, was effective and safe in hyperlipidemia treatment. TC, LDL-C, and TG were statistically significantly reduced, and HDL-C was increased at the end of the study. The results were similar in the Slovenian and the Slovakian studies (**Figure 1**):

- In the Slovenian study, where the mean dose was 17.3 mg, the mean reductions were the following: TC by 29.6%, LDL-C by 39.2%, TG by 26%, while HDL-C increased by 3.7%.
- In the Slovakian study, where the mean dose was 19.3 mg, the mean reductions were the following: TC by 21.2%, LDL-C by 30.6%, TG by 21%, while HDL-C increased by 6.2%.

A linear relationship between the dose and the LDL-C reduction was thus established (**Figure 2**).

In both studies (**Figure 3**), the overall treatment outcome with Krka's rosuvastatin was assessed as very successful if the target LDL-C was reached (LDL-C ≤ 2.99 mmol/L in primary prevention or LDL-C ≤ 2.49 mmol/l in secondary preven-

FIGURE 2.

Mean change in LDL-C levels resulting from increasing the dose of rosuvastatin

Person's r = 0.1171 (asymptotic confidence interval: 0.0888–1.465).

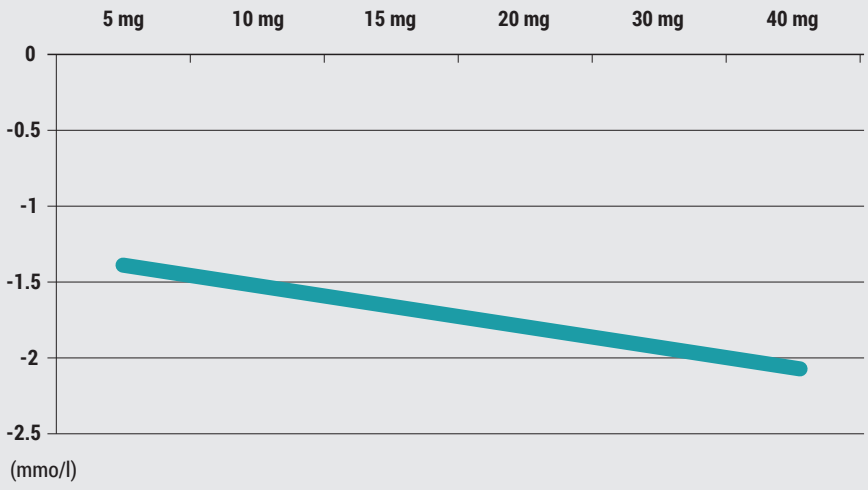
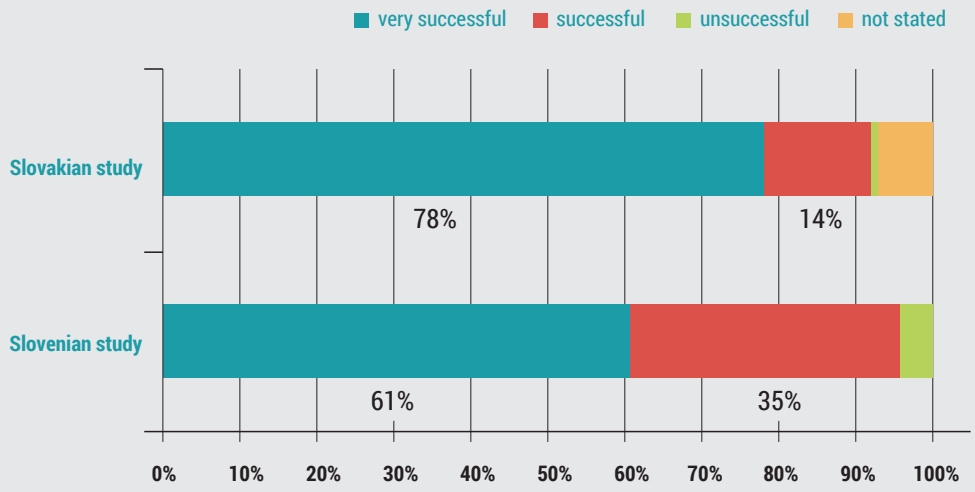


FIGURE 3.

Clinical efficacy in the Slovenian and the Slovakian study.



nost LDL-C smanjena za manje od 10% ili ako nije bilo promjene u usporedbi s početnom razinom LDL-C.

- U slovenskoj studiji, opća uspješnost Krkinog rosuvastatina procijenjena je kao vrlo uspješna ili uspješna za 96% slučajeva.
- U slovačkoj studiji, rezultati liječenja za 92% pacijenata procijenjeni su kao vrlo uspješni ili uspješni.

S učestalošću neželjenih reakcija nižom od 3% kroz cijelu studiju, Krkin rosuvastatin pokazao se kao veoma siguran i učinkovit statin; 97,3% pacijenata u slovenskoj studiji i 99% pacijenata u slovačkoj studiji nije imao nikakve neželjene reakcije.

Postautorizacijske studije na gotovo 7.000 pacijenata pokazale su dobru podnošljivost i potvrdile očekivanu učinkovitost Krkinog rosuvastatina (Roswera®), uključujući nove jačine doza od 15 mg i 30 mg. Uz to, uspostavljena je linearna povezanost između doza i smanjenja razine LDL-C. Širok raspon jačina Krkinog rosuvastatina omogućuje prilagođavanje liječenja individualnim potrebama bolesnika i povećava postotak pacijenata koji dostižu ciljne razine lipida.

tion), as successful if LDL-C was reduced by more than 10% but the target values were not reached, and as unsuccessful if LDL-C was reduced by less than 10% or there was no change compared with the baseline LDL-C levels.

- In the Slovenian study, the overall clinical efficacy of Krka's rosuvastatin was assessed as very successful or successful in 96% of the cases.
- In the Slovakian study, treatment outcomes in 92% of the patients were assessed as very successful or successful.

With the total incidence of adverse reactions of less than 3% throughout the course of the study, Krka's rosuvastatin was proven to be a very safe and effective statin; 97.3% of the patients in the Slovenian study and 99% of the patients in the Slovakian study had no adverse reactions.

Post-authorisation studies in almost 7.000 patients have demonstrated good tolerability and confirmed the expected efficacy of Krka's rosuvastatin (Roswera®), including its new 15 mg and 30 mg dosage strengths. In addition, a linear relationship between the dose and the reduction of the LDL-C level was established. The wide range of dosage strengths of Krka's rosuvastatin allows treatment to be adjusted to the requirements of individual patients and increases the percentage of patients that reach their target lipid levels.

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