Rosuvastatin has therapeutic potential in patients after heart transplantation

Luknar M[1], Lesny P[1], Varga I[1], Solik P[1], Kucerova D[1], Danova K[2]

[1]*Heart Failure and Transplant Department, National Cardiovascular Institute, Bratislava, Slovakia*

Luknar M, Lesny P, Varga I, Solik P, Kucerova D, Danova K. **Rosuvastatin has therapeutic potential in patients after heart transplantation.** Cardiology Lett. 2012;21(6):469–473

Abstract. *Background:* Heart transplant (HTx) recipients are at high cardiovascular risk and strict risk factor control is warranted. Hypercholesterolemia is frequent after HTx and statins are routinely administered. Statins, however, are linked to a substantial risk of harmful side effects. Rosuvastatin has been proven effective and safe in the general population. Data on rosuvastatin use in HTx recipients are scarce. We evaluated the safety of rosuvastatin and its influence on blood lipids in patients after HTx.

Patients and methods: Sixteen HTx recipients with inadequate hypolipidemic response to fluvastatin 80 mg (median age 57 (36-60) years, 11 men) were evaluated. All patients received a combined immunosuppressive regimen. Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triacylglycerole (TAG) levels were determined at initial evaluation. Subsequently, open-label rosuvastatin 10 mg/day was initiated and fluvastatin was stopped. After a median 12 (4-24) weeks, the same parameters were measured. Clinical adverse events were reported and blood levels of creatine phosphokinase, myoglobin, and aminotransferases were determined. Differences between baseline and on-rosuvastatin lipid levels were assessed by Wilcoxon paired test.

Results: After rosuvastatin use, TC decreased from 6.22±0.70 mmol/L to 5.45±0.88 mmol/L ($p<0.05$). LDL cholesterol dropped from 3.69±0.76 mmol/L to 2.93±0.76 mmol/L ($p=0.02$). Increase in HDL-C and decrease in TAG levels were not statistically significant. Only 2 patients reached TC levels <4.5 mmol/L and 4 reached LDL values <2.5 mmol/L. No serious clinical and laboratory adverse effects or significant change in immunosuppressant level were recorded.

Conclusion: Rosuvastatin 10 mg was safe and effective in HTx recipients with sub-optimal lipid levels on their previous statin treatment. However, reaching targets recommended for high-risk populations probably requires higher doses. Determination of long-term safety and efficacy of such doses, and their influence on morbidity and mortality, warrants further study. Fig. 1, Tab. 1, Ref. 17, Online full text (Free, PDF) www.cardiology.sk

Key words: rosuvastatin – heart transplantation – statins – hypercholesterolemia – hypolipidemic treatment

Luknár M, Lesný P, Varga I, Solík P, Kučerová D, Daňová, K. **Rosuvastatín má terapeutický potenciál u pacientov po transplantácii srdca.** Cardiology Lett. 2012;21(6):469–473

Abstrakt. *Úvod:* Pacienti po transplantácii srdca (HTx) sa vyznačujú vysokým kardiovaskulárnym rizikom. Potrebná je prísna kontrola rizikových faktorov. Hypercholesterolémia po HTx je častá a v liečbe sa rutinne používajú statíny, ktoré sa však spájajú s významným rizikom nežiaducich účinkov. Rosuvastatín sa vo všeobecnej populácii ukázal ako účinný a bezpečný. Údajov o používaní rosuvastatínu u pacientov po transplantácii srdca je málo. Hodnotili sme bezpečnosť rosuvastatínu a jeho vplyv na lipidové parametre u pacientov po HTx.

Pacienti a metódy: Sledovali sme 16 pacientov po HTx s nedostatočnou hypolipidemickou reakciou na fluvastatín v dávke 80 mg [medián veku 57 (36 – 60) rokov, 11 mužov]. Všetci pacienti užívali kombinovanú

From [1]Heart Failure and Transplant Department and [2]Department of Laboratory Medicine, National Cardiovascular Institute, Bratislava, Slovakia
Manuscript received August 6, 2012; accepted for publication October 17, 2012

Address for correspondence: Milan Luknár, MD, Heart Failure and Transplant Department, National Cardiovascular Institute, Pod Krásnou Hôrkou 1, 833 48 Bratislava, e-mail: luknar@nusch.sk

imunosupresívnu liečbu. Pri vstupnom vyšetrení sme stanovili hodnoty celkového cholesterolu (TC), cholesterolu lipoproteínov s nízkou hodnotou (LDL-C), cholesterolu lipoproteínov s vysokou hodnotou hustoty (HDL-C) a triacylglycerolov (TAG). Následne sme iniciovali liečbu rosuvastatínom v dávke 10 mg/deň a ukončili sme podávanie fluvastatínu. Po období s mediánom 12 (4 – 24) týždňov sme stanovili tie isté ukazovatele. Zaznamenali sme klinické nežiaduce príhody, ako aj hodnoty kreatínkinázy, myoglobínu a aminotransferáz. Rozdiely medzi koncentráciami lipidových parametrov medzi vstupným a kontrolným vyšetrením sme štatisticky hodnotili pomocou Wilcoxonovho párového testu.
Výsledky: Po podávaní rosuvastatínu klesli hodnoty TC z 6,22 ± 0,70 mmol/l na 5,45 ± 0,88 mmol/l (p < 0,05). LDL cholesterol klesol z 3,69 ± 0,76 mmol/l na 2,93 ± 0,76 mmol/l (p = 0,02). Vzostup koncentrácií HDL-C a pokles TAG neboli štatisticky významné. Len dvaja pacienti dosiahli hodnoty TC < 4,5 mmol/l a štyria dosiahli hodnoty LDL < 2,5 mmol/l. Nezaznamenali sa žiadne významné klinické ani laboratórne nežiaduce účinky a signifikantné zmeny koncentrácií imunosupresív.
Záver: Rosuvastatín v dávke 10 mg bol u pacientov po HTx so suboptimálnymi hodnotami lipidov pri predchádzajúcej liečbe statínom bezpečný a účinný. Dosiahnutie cieľových hodnôt odporúčaných pre vysokorizikovú populáciu si však pravdepodobne vyžaduje vyššie dávky rosuvastatínu. Na stanovenie dlhodobej bezpečnosti a účinnosti takýchto dávok a ich vplyv na morbiditu a mortalitu je potrebný ďalší výskum. Obr. 1, Tab. 1, Lit. 17, Online full text (Free, PDF) www.cardiology.sk
Kľúčové slová: rosuvastatín – transplantácia srdca – statíny – hypercholesterolémia – hypolipidemická liečba

Heart transplant (HTx) recipients are at high risk of cardiovascular events due to coronary artery vasculopathy (CAV), ischemic stroke, and peripheral artery disease (1). Hypercholesterolemia is an established cardiovascular risk factor and also seems to play a role in CAV development (2). The prevalence of hyperlipidemia among HTx recipients is as high as 95% at 5 years after their transplant (1).

Statins have become a standard treatment component after HTx. Even though a "normal" range of lipid parameters in this specific population has not yet been determined, and thus target and safe cholesterol values with statin treatment are not known, statins have been proven to prevent the progression of graft vascular disease, to decrease the incidence of acute rejection, and to improve survival in HTx recipients (3 – 5). Due to their pharmacokinetic interactions and pharmacodynamic effects, statins, in particular simvastatin and atorvastatin, are linked to severe adverse events (6). Rosuvastatin has been established as an effective hypolipidemic agent in the general population (7). Data on rosuvastatin use after HTx are scarce. Due to its metabolism, which is independent of the CYP3A4 (8) pathway and theoretically does not interfere with the metabolism of calcineurin inhibitors, rosuvastatin could be a safe hypolipidemic option after HTx.

We tried to determine the safety of rosuvastatin and its efficacy in terms of lipid lowering in HTx recipients with insufficient hypolipidemic response to their previous statin treatment.

Patients and methods

Twenty-three HTx recipients with no significant rejection in the past six months and with inadequate hypolipidemic response to statins, according to their medical records, were screened. Blood samples were drawn at initial evaluation. Patients with total cholesterol (TC) level ≥5.0 mmol/L or low-density lipoprotein cholesterol (LDL-C) level ≥3.0 mmol/L on their current statin treatment were eligible to enter the study. Patients with cholesterol levels below these values were excluded. Inclusion criteria were fulfilled by sixteen patients. Median age of the group was 57 (36-60) years; 11 were men. Median time from HTx was 20 (6-178) months. Eight patients received tacrolimus and 8 ciclosporin, three were on everolimus. Thirteen patients were administered mycophenolate mofetil and 14 prednisone. These medications and their doses remained the same throughout the study period. As hypolipidemic treatment, all patients received slow release fluvastatin 80 mg, and one received ezetimibe as additional medication.

At initial evaluation, patients underwent clinical examination and laboratory parameters were determined. Efficacy parameters included TC, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triacylglycerole (TAG) levels. LDL-C was calculated according to the Friedewald formula (9). No patients were excluded from LDL-C analysis owing to increased TAG values that would preclude correct LDL-C calculation. Safety endpoints included clinical events of myalgia, plasma aminotransferase and creatin kinase activities, and creatinine and myoglobin levels. Blood for laboratory tests was drawn in the office of a specialized HTx centre, in the morning, after at least 12 hour fasting. As the patients had been receiving healthy lifestyle and dietary advice since their transplant, no further lifestyle or diet modification was proposed at the time of rosuvastatin initiation. Baseline patient characteristics are shown in **Table 1**.

Open-label oral rosuvastatin 10 mg was initiated in eligible patients after the initial examination, and fluvastatin was ceased at the same time. The patients were instructed to

take rosuvastatin in the evening with their other medication. After a median 12 (4-24) weeks, clinical examination was performed and the same parameters were determined under identical conditions.

The Wilcoxon pair test was used to test the statistical significance of differences between lipid levels before and after rosuvastatin treatment (using Primer of Biostatistics, statistical software program version 5.0, Mc Graw Hill, 2001).

Results

After switch from fluvastatin 80 mg to rosuvastatin 10 mg, TC levels decreased from 6.22±0.70 mmol/L to 5.45±0.88 mmol/L ($p<0.05$). LDL cholesterol dropped from 3.69±0.76 mmol/L to 2.93±0.76 mmol/L ($p=0.02$). Increase in HDL-C and decrease in TAG levels were not statistically significant (1.32±0.34 vs. 1.41±0.49 mmol/L, and 2.78±0.91 vs. 2.27±0.88 mmol/L, resp., p=n. s. for both). 2 patients reached TC levels <4.5 mmol/L and 4 reached LDL values <2.5 mmol/L.

No serious adverse effects were reported by patients. There were no significant laboratory abnormalities, nor any case of treatment cessation necessary. There was one episode of transient myalgia that resolved spontaneously, and one mild increase in aminotrasferases <3x upper limit of normal range. There was no case of creatine phosphokinase or myoglobin level increase over upper level of normal range, nor any creatinine and BUN increase. In three patients there was an increased immunosuppressant (in 2 cases ciclosporin and in 1 tacrolimus) level that required subsequent respective dose adjustment after the end of the study. The results are summarized in **Figure 1**.

Table 1 Patient characteristics at baseline

Number		16
men		11
Age (median, range) [years]		57 (36-60)
Time from transplant (median, range) [months]		48.8 (6-178)
Immunosuppressive treatment (n)	tacrolimus	8
	ciclosporin	8
	mycophenolate mofetil	13
	everolimus	3
	prednisone	14
Hypolipidemic treatment (n)	fluvastatin 80 mg	16
	ezetimibe	1

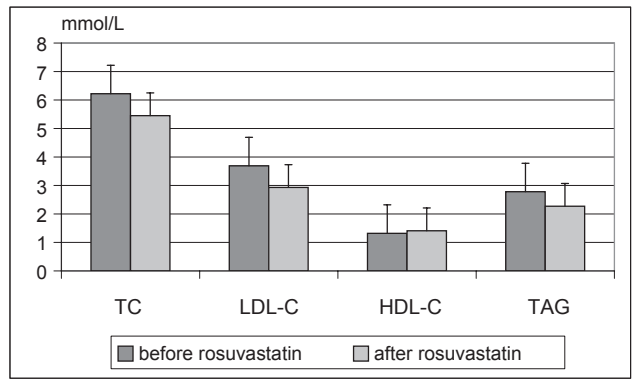

Figure 1 Lipid levels before and after rosuvastatin treatment
TC – total cholesterol, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, TAG – triacylglyceroles

Discussion

The rationale for statin administration after HTx is based on several assumptions. Statins have shown a positive effect on mortality in this population and which was independent of their lipid-lowering effect (3 – 5). On the other hand, while etiology and pathogenesis of coronary allograft vasculopathy differs from coronary heart disease in the native heart (10), hypercholesterolemia has been linked to graft vascular disease (2). Regarding their 10-year cumulative risk of fatal cardiovascular events (including stroke), HTx recipients represent a high-risk population and according to traditional risk schemes for general population, such patients should be treated to strict target values (11). European Society of Cardiology guidelines, although providing some recommendations for treatment of hypolipidemia in transplant recipients, do not specify efficient and safe target values for this subset of patients (11).

Rosuvastatin showed a good efficacy in terms of lipid lowering effect as well as on morbidity and mortality across the whole array of cardiovascular risk (7). Its efficiency in terms of morbidity and mortality reduction after HTx has not been published. The pharmacokinetics of rosuvastatin avoids the CYP3A4 pathway (8). Rosuvastatin appears to be safer than other statins used in contemporary clinical practice (12), which could be an advantage in patients on such drugs as ciclosporin and tacrolimus, and so rosuvastatin is considered a drug of choice in patients after HTx (13).

Our group consisted of patients who had failed to reach treatment goals with fluvastatin. In our centre fluvastatin is routinely used in HTx recipients from the early post-operation period. We have preferred fluvastatin due to safety reasons. Some comparisons showed a lower hypolipidemic potential of fluvastatin relative to other statins (14). Mean baseline values of TC and LDL-C in our group of patients treated with fluvastatin 80 mg were 6.22±0.70 and 3.69±0.76 mmol/L, resp., which is far from optimal for this high-risk population. Rosuvastatin-treated patients, on the other hand, demonstrated a significantly lower rate of failure in achieving the therapeutic goal than patients treated with other statins including fluvastatin in one retrospective analysis of hypolipidemic treatment resistant patients (15).

We have found only one full text report on rosuvastatin use after HTx. An open-label study with rosuvastatin in HTx recipients by Samman et al. (16) involved 21 patients. These patients were older than our group (median 66 vs. 57 years). The rate of tacrolimus use in this group was lower than in our group (19% vs. 50% in our group), and prednisone use was also less frequent (24% vs. 88% in our group). Doses of rosuvastatin were adjusted (5-20 mg/day according to previous statin doses), while the rosuvastatin dose in our patients was fixed (10 mg/day). The duration of follow-up was longer in our group (median 12 vs. 6 weeks).

Samman et al. (16) reported a significant decrease in TC, HDL-C, and TAG levels. 70% of their patients reached an LDL-C level of <2.5 mmol/L. Although we found a statistically significant drop in TC and LDL-C concentrations, only 4 of our 16 patients reached this specific target. Only 2 of our patients achieved the target values recommended for high-risk population, i. e. TC of 4.5 mmol/L. A less strict target of ≤5.2 mmol/L was reached by 80% of patients from Samman's group.

Traditional risk scoring systems do not provide HDL-C and TAG goals for high-risk groups. However, HDL-C level <1.17 mmol/L serves as a marker of increased cardiovascular risk and TAG concentrations <1.7 mmol/L are desirable (11). Mean initial HDL-C level exceeded this value in our patients and did not change significantly after rosuvastatin administration. Initial TAG levels were in the higher-risk stratum and remained significantly unchanged, in contrast to the results of Samman et al. who found a significant TAG concentration decrease.

According to some reports, rosuvastatin should be used with caution in patients after organ transplantation treated by ciclosporin (17). In one pharmacokinetic study, rosuvastatin exposure was significantly increased in HTx recipients on ciclosporin, supposedly due to ciclosporin inhibition of organic anion transporting polypeptide (OATP-C)-mediated rosuvastatin hepatic uptake (17). Rosuvastatin had no significant influence on ciclosporin concentrations in our study. We found a mildly increased concentration of calcineurin inhibitors in 3 of 16 patients after rosuvastatin administration. Although these small numbers preclude more detailed conclusions, as calcineurin inhibitor concentrations can be influenced by several mechanisms, we believe a 10 mg dose of rosuvastatin does not result in a clinically significant increase in calcineurin inhibitor levels.

Although we found that mean TC and LDL-C concentrations had dropped, most of our patients did not reach treatment targets for a high-risk population. This implies that these patients, who previously had not shown a satisfactory response to other statins, probably require higher doses of rosuvastatin. Finding the effective dose of rosuvastatin was not the aim of our study. Adverse clinical and laboratory effects of higher doses can significantly differ from those of the lower doses used in this study. We neither evaluated the clinical effectiveness of rosuvastatin on cardiovascular mortality, nor morbidity and global long-term safety in patients with lower lipid values. The study was not powerful enough to compare different subgroups of HTx recipients.

Study limitations. We are aware that this study has several limitations. The first one is the small number of patients and the single-centre character of the study. Thus no subgroup analysis was possible. This study lacks a control group and medication was open to patients and treating physicians. Adherence and compliance to the medication were not verified.

In conclusion, rosuvastatin 10 mg was safe and effective in a real-life population of HTx recipients with sub-optimal lipid levels on their previous statin treatment. However, most of the patients did not achieve target lipid values recommended for the high-risk non-transplant population. Reaching these targets probably requires higher rosuvastatin doses. Determination of long-term efficacy of rosuvastatin in different doses, as well of its influence on cardiovascular morbidity and mortality, and long-term safety evaluation, require further study.

Acknowledgements

The authors would like to thank Ass. Prof. Eva Goncalvesova, MD, PhD, for her long-term and systematic medical mentoring and scientific leadership.

References

1. Stehlik J, Edwards LB, Kucheryavaya A, et al. The Registry of the International Society for Heart and Lung Transplantation: Twenty-eight adult heart transplant report–2011. J Heart Lung Transplant 2011;30(10):1078-1094.
2. Chamorro CI, Almenar L, Martínez-Dolz L, et al. Do cardiovascular risk factors influence cardiac allograft vasculopathy? Transplant Proc 2006;38(8):2572-2574.
3. Kobashigawa JA, Moriguchi JD, Laks H, et al. Ten-year follow-up of a randomized trial of pravastatin in heart transplant patients. J Heart Lung Transplant 2005;24(11):1736-1740.
4. Wenke K, Meiser B, Thiery J, et al. Simvastatin reduces graft vessel disease and mortality after heart transplantation: a four-year randomized trial. Circulation 1997;96:1398–1402.
5. Carrier M, Rivard M, Kostuk W, et al. The Canadian Study of Cardiac Transplantation. Atherosclerosis. Investigators of the CASCADE Study. Can J Cardiol 1999;15(12):1337-1344.
6. Ballantyne CM, Corsini A, Davidson MH, et al. Risk for myopathy with statin therapy in high-risk patients. Arch Intern Med 2003;163(5):553-64.
7. Barrios V, Escobar C. Rosuvastatin along the cardiovascular continuum: from JUPITER to AURORA. Expert Rev Cardiovasc Ther 2009;7(11):1317-1327.

8. McTaggart F, Buckett L, Davidson R, et al. Preclinical and clinical pharmacology of Rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. Am J Cardiol 2001;87(5A):28B-32B.
9. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of the low-density lipoprotein cholesterol in plasma without the use of preparative ultra centrifugation. Clin Chem 1972;18:499–509.
10. Goncalvesova E. The vascular graft disease – pathomorphology and etiopathogenesis. Cardiol 2000; 9(5):274–279.
11. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011;32:1769–1818.
12. Garcia-Rodríguez LA, Massó-González EL, Wallander MA, et al The safety of rosuvastatin in comparison with other statins in over 100,000 statin users in UK primary care. Pharmacoepidemiol Drug Saf 2008;17(10):943-952.
13. Špinarová L, Vítovec J. Statiny a srdeční transplantace. Remedia 2005:15(2):154-157.
14. Jones P, Kafonek S, Laurora I, et al. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). American J Cardiol 1998;81:582-587 [erratum in Am J Cardiol 1998:82(1):128].
15. Harley CR, Gandhi S, Heien H, et al. The comparative effectiveness of rosuvastatin vs. other statins in patients with an increased risk of failure to reach NCEP ATP III goal. Int J Clin Pract 2008;62(6):889-895.
16. Samman A, Imai C, Straatman L, et al. Safety and efficacy of rosuvastatin therapy for the prevention of hyperlipidemia in adult cardiac transplant recipients. J Heart Lung Transplant 2005;24:1008-1013.
17. Simonson SG, Raza A, Martin PD, et al. Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine. Clin Pharmacol Ther 2004;76(2):167-177.