Non–Daily-Dosed Rosuvastatin in Statin-Intolerant Veterans

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In this single center, retrospective chart review, the authors evaluate the safety and effectiveness of non–daily-dosed rosuvastatin in veterans with a previous statin intolerance.

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, are the treatment of choice for hyperlipidemia.[1] Many patients, however, are unable to tolerate statins and subsequently discontinue therapy. The reported incidence of statin intolerance varies widely in the literature. A recent review estimated that 10% to 15% of statin users experience some type of myopathy, which is one of the most common reasons for discontinuation.[2] Other reasons for discontinuation include diarrhea, nausea, constipation, headache, dizziness, mental confusion, forgetfulness, erectile dysfunction, and elevated hepatic enzymes.[3]

Various recommendations exist for alternative therapies for statin-intolerant patients. These recommendations include using alternative medications, such as ezetimibe, bile acid sequestrants, or red yeast rice. Other recommendations include intensifying lifestyle changes, trying a different statin, reducing the daily statin dose, rechallenging the statin at a lower daily dose after a statin-free period, switching to fluvastatin XL daily, or switching to another statin at a low daily dose or on alternate days of the week.[3,4]

Considering the proven cardiovascular benefits of statin therapy, it would be reasonable to attempt continuation of statin therapy before switching to a nonstatin therapy.[1] Non–daily-dosed rosuvastatin may be a therapeutic alternative, because it has a longer terminal half-life compared with other statins.[5] Some providers at the Southern Arizona VA Health Care System (SAVAHCS) implement nondaily rosuvastatin for patients previously intolerant to daily statin therapy. Clinical pharmacists are among some of these providers. Clinical pharmacists at SAVAHCS manage lipid therapy in a collaborative practice agreement with primary care providers, cardiologists, and other providers. Providers can consult pharmacists, and pharmacists manage lipids with a low-density lipoprotein cholesterol (LDL-C) goal that was either specified by the provider or determined by the pharmacist, based on the National Cholesterol Education Program (NCEP) guidelines.

Few studies exist that evaluate non–daily-dosed statins in patients with a previous statin intolerance. One of the first case reports was in 2007. The authors reported on 2 patients previously intolerant to once-daily atorvastatin who were switched to rosuvastatin dosed on Mondays, Wednesdays, and Fridays.[6] Both patients experienced resolution of adverse effects (AEs) and significant decreases in LDL-C, triglycerides (TG), and total cholesterol (TC). Another article in 2007 reported 10 patients who were intolerant of once–daily-dosed statins.[7] These patients were prescribed once-weekly rosuvastatin, and 8 of the 10 patients tolerated the therapy. These 8 patients experienced an average reduction in LDL-C of 28%. These case reports suggested the potential role of alternate-day dosing of statins.

There are 3 published retrospective studies and 1 prospective study that evaluate nondaily rosuvastatin in previously statin-intolerant patients. In a 2008 retrospective study by Gadarla and colleagues, 40 patients were treated with rosuvastatin 5 mg to 10 mg twice weekly.[8] Eighty percent of these patients tolerated the therapy, mean LDL-C was reduced by 43 ± 26 mg/dL (26%), and 54% of these patients reached their LDL-C goals. A second 2008 retrospective study by Backes and colleagues included 51 patients who received rosuvastatin 2.5 mg to 10 mg every other day.[9] Seventy-two percent of these patients tolerated therapy, mean LDL-C was

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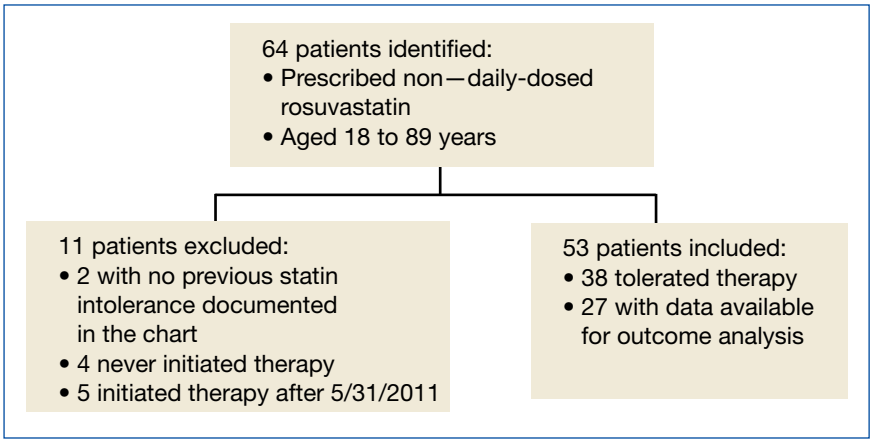

Figure 1. Patient Distribution.

reduced by 34.5%, and 50% of these patients reached their LDL-C goals. A third study published in 2009 by Ruisinger and colleagues included 50 patients who were prescribed rosuvastatin 2.5 mg to 20 mg once weekly.[10] Seventy-four percent of these patients tolerated the therapy, and mean LDL-C was reduced by 23%. Last, Kennedy and colleagues published a prospective study in 2011.[11] This study was a randomized, double-blind, placebo-controlled crossover trial that evaluated 17 statin-intolerant patients. The patients in this study received rosuvastatin 5 mg once weekly or a matching placebo. This study found that 80% of the patients in the rosuvastatin group tolerated the therapy (vs 88% in the placebo group), mean LDL-C was reduced by 12.2% in the rosuvastatin group (vs 0.4% in the placebo group), and 20% of the patients in the rosuvastatin group reached their LDL-C goals (vs 0% in the placebo group). These studies concluded that the alternate-day dosing of rosuvastatin improved lipid profiles and was a well-tolerated dosing strategy. This study examined previously statin-intolerant veterans who were initiated on non–daily-dosed rosuvastatin therapy, which was often titrated to an effective dose that was well tolerated.

METHODS

This study was a retrospective chart review. Approval was received from the Institutional Review Board at the University of Arizona and the Research and Development Committee at SAVAHCS. Patients receiving non–daily-dosed rosuvastatin between January 1, 2009, and July 31, 2011, were evaluated. Electronic medical records (EMRs) at SAVAHCS were reviewed for inclusion and exclusion criteria. Patients were included in this study if they were prescribed non–daily-dosed rosuvastatin (ie, once weekly, twice weekly, 3 times weekly) and were aged 18 to 89 years. Patients were excluded from this study if they had been on non–daily-dosed rosuvastatin for < 8 weeks before the end of the study period or if a previous intolerance to at least 1 daily-dosed statin was not documented in the EMR. Data up to July 31, 2011, were recorded.

For subjects who met the criteria, data collected included information about the previous statin intolerance, including the specific statin and intolerance experienced. The type of provider who managed lipid-lowering therapy, rosuvastatin dose and dosing frequency, tolerability, and

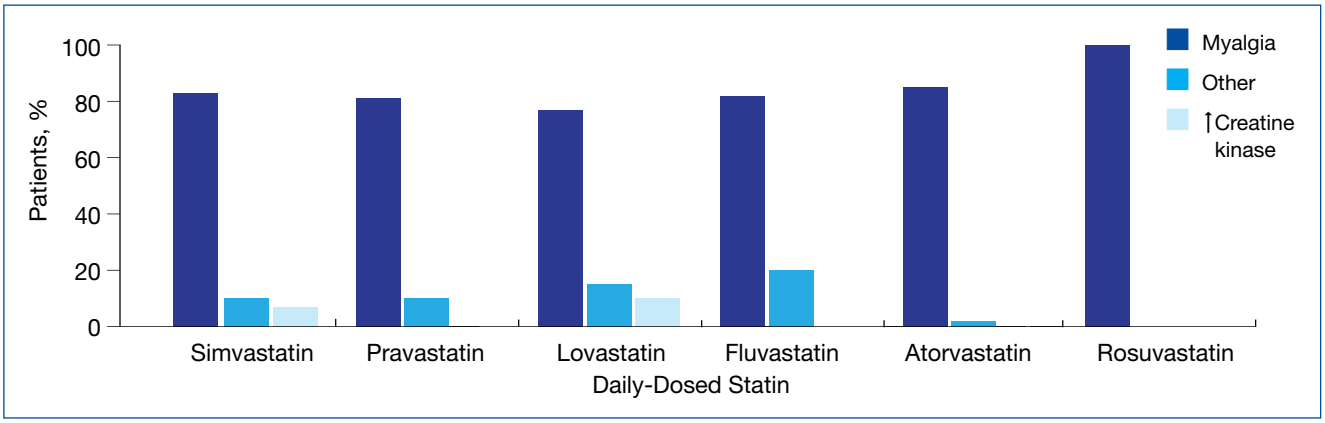

Figure 2. Previous Statin Intolerance (n = 53).

titration information for all patients was recorded. Tolerability was defined as continuation of therapy through the end of the study period. Other data collected included concomitant lipid-lowering agent(s) and laboratory values (serum lipids, liver enzymes, and creatine kinase [CK]) at predetermined points during the study period.

The subject's LDL-C goal was determined according to the patient's risk factors as outlined in the NCEP guidelines.[12] This was recorded as the NCEP LDL-C goal. In addition, if the provider specified an LDL-C goal, this was recorded as the non-NCEP LDL-C goal. The NCEP LDL-C goal was different from the non-NCEP LDL-C goal, because some providers used a more stringent goal of < 70 mg/dL, according to the American Heart Association and the American College of Cardiology.[13] Both LDL-C goals were used in the analyses.

The primary outcome measured in this study was whether the patients met the LDL-C goal on nondaily rosuvastatin. Secondary outcomes included mean changes in TC, LDL-C, high-density lipoprotein cholesterol (HDL-C), and TG; the overall safety and tolerability of therapy; and whether patients met the LDL-C goal stratified by the provider who managed the lipid-lowering therapy. The primary outcome was analyzed using descriptive statistics. Mean changes in serum lipids were analyzed using a paired Student's *t* test, and other secondary outcomes were analyzed using descriptive statistics.

RESULTS

A total of 64 patients were identified as being prescribed non–daily-dosed rosuvastatin. Eleven of these 64 patients were excluded. Four patients never initiated nondaily rosuvastatin, 2 had no previous statin intolerance documented, and 5 initiated therapy < 8 weeks before the end of the study period (Figure 1). A total of 53 patients were included in this study. The majority of the patients were male (96%), the average age was 69 years, and 72% of the patients tolerated therapy. Previous intolerances to daily-dosed statins are shown in Figure 2. Many patients experienced intolerances to multiple daily-dosed statins, and some patients experienced multiple AEs to each statin. The most common intolerance across all statins was myalgia. Other intolerances comprised mainly gastrointestinal AEs and elevated liver function tests (LFTs).

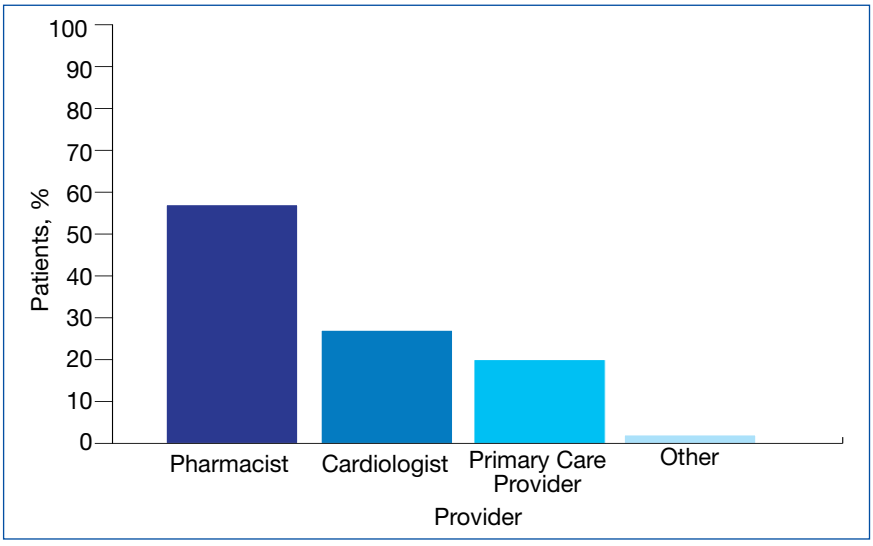

Figure 3. Providers Managing Therapy (n = 53).

The providers who managed the nondaily rosuvastatin therapy included clinical pharmacists (55%), cardiologists (25%), primary care providers (PCPs) (19%), and other providers (2%) (Figure 3). Of the patients that tolerated the therapy, only 27 had data available for primary and secondary outcome analysis data. Eighty-five percent of these patients were above the NCEP LDL-C goal at baseline, and 20 patients had a provider-established non-NCEP LDL-C goal recorded in the EMR.

Sixteen of the 27 patients (59%) achieved the NCEP LDL-C goal, and 10 of the 20 patients (50%) achieved the provider-established non-NCEP LDL-C goal. There were 3 patients who met the NCEP LDL-C goal but did not meet a more stringent non-NCEP LDL-C goal.

There was a statistically significant reduction in TC and LDL-C by 20% and 31%, respectively ($P < .0001$) (Table). The average TC level decreased from 219 mg/dL to 177 mg/dL, and the average LDL-C level decreased from 144 mg/dL to 99 mg/dL. There were no significant changes in the HDL-C or TG levels.

Of the 53 patients included in this study, 15 were unable to tolerate the therapy and subsequently discontinued. The most common reason for discontinuation was myalgia (n = 9), and other reasons (n = 6) included gastrointestinal pain, elevated liver enzymes, and unknown/undocumented (Figure 4). There were no significant elevations in liver enzymes or in CK. It was reported that 2 patients discontinued the therapy due to elevated liver enzymes; however, the documented LFTs were < 3 times

Table. Change in Serum Lipids (n = 27)

Measure	Baseline (mg/dL) ± SD	Follow-up (mg/dL) ± SD	Change (mg/dL)[a]	*P* value
TC	219 ± 49.0	177 ± 39.9	-42 (20)	< .0001
LDL-C	144 ± 43.2	99 ± 33.8	-45 (31)	< .0001
HDL-C	42 ± 9.9	41 ± 10.6	+1 (2)	= .393
TG	168 ± 67.8	181 ± 151.6	+13 (8)	= .318

[a]Numbers in parentheses are percentages.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation; TC = total cholesterol; TG = triglycerides.

the upper limit of normal. There were 4 cases of mild elevations in CK with levels ranging from 159 units/L to 367 units/L. Three of the 4 patients tolerated and continued the therapy. The other patient discontinued the therapy, but for a different reason.

The primary outcome was further stratified by provider. Of the 27 patients with data available for outcomes, 17 were managed by a pharmacist, 5 by a cardiologist, and 4 by a PCP. Thirteen (76%) of the 17 pharmacist-managed patients met the NCEP goal, 1 (20%) of the 5 cardiologist-managed patients met the NCEP goal, and 2 (40%) of the 5 PCP-managed patients met the NCEP goal. Twenty out of these 27 patients had a provider-established non-NCEP goal. Of these 20 patients, 16 were managed by a pharmacist, 3 by a cardiologist, and 1 by a PCP. Nine (56%) of the 16 pharmacist-managed patients met the non-NCEP goal, none of the 3 cardiologist-managed patients met the non-NCEP goal, and 1 (100%) of the 1 PCP-managed patient met the non-NCEP goal.

Concomitant lipid-lowering therapy was evaluated. There were 13 patients (48%) on a concomitant agent with no change throughout the study. The most common agent was fish oil or omega-3-fatty acids (n = 6), and other agents included niacin (n = 2), fenofibrate (n = 1), fenofibrate plus ezetimibe (n = 1), niacin plus ezetimibe (n = 1), and niacin plus fish oil/omega-3-fatty acids (n = 1). There were 3 patients (11%) who initiated a concomitant agent during the study period. These agents included niacin (n = 1), gemfibrozil (n = 1), and fenofibrate (n = 1). Last, there were 6 patients (22%) who discontinued a concomitant agent during the study period. These agents included niacin (n = 2), cholestyramine (n = 2), pravastatin (n = 1), and gemfibrozil plus fenofibrate (n = 1).

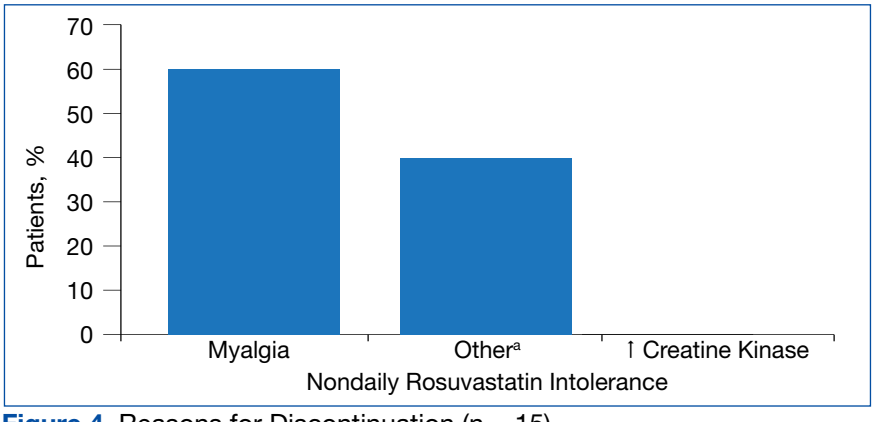

Figure 4. Reasons for Discontinuation (n = 15).

[a]Other reasons include gastrointestinal pain, elevated liver function tests, and unknown.

The most frequent starting dose was 5 mg per week with doses in the range of 2.5 mg once weekly to 40 mg every other day. The average starting dose was 15 mg ± 21.1 mg per week. Therapy was titrated up in 45% of the patients, and there were 5 patients who were titrated up to daily-dosed rosuvastatin. At the end of the study period, for those patients who continued and tolerated therapy, the most frequent dose was 10 mg per week with doses in the range of 5 mg once weekly to 40 mg daily. The average dose at the end of the study period was 28 mg ± 48 mg per week.

DISCUSSION

Daily-dosed statin therapy may not be tolerated by some patients. The findings of this study suggest that nondaily rosuvastatin is an effective alternative statin therapy in these patients. Seventy-two percent tolerated the nondaily therapy. Significant reductions in TC and LDL-C occurred, and 59% of the patients met their LDL-C goals. These findings are consistent with other published studies.

The tolerability of statins may be improved with this alternative dosing strategy for several reasons. One explanation may be that nondaily dosing leads to lower drug concentration levels and thus fewer AEs. Another explanation may be that by starting at a lower dose and slowly titrating, the dose allows for improved tolerance. Several patients in this study were able to tolerate being titrated up to a daily rosuvastatin dose.

This alternative therapy appears to

be a safe therapy, because there were no serious AEs reported in this study population. There were no significant elevations in liver enzymes. This is consistent with the recent U.S. Food and Drug Administration (FDA) labeling changes for statin therapy. The FDA has stated that liver injury is rare, and LFT monitoring is not necessary other than at baseline and if liver injury is suspected.[14] There also were no significant elevations in CK, although this was not frequently monitored. The most common reason for discontinuation of nondaily rosuvastatin was myalgia. This was expected, because most of these patients experienced myalgia to daily-dosed statins before being prescribed nondaily rosuvastatin.

This study looked at patients who met their LDL-C goals and stratified it by the provider who managed the lipid-lowering therapy. It was found that more pharmacist-managed patients met their LDL-C goals compared with other providers. This may be explained by the frequent follow-up and close monitoring the patients have with the pharmacists at SAVAHCS. The pharmacists have a collaborative practice agreement with providers to manage lipid-lowering therapy.

LIMITATIONS

There are several limitations to this study. It was a retrospective study, and data collection relied on the accuracy of the EMR. The majority of the veterans in this study were male, and the results may not be generalized to a larger population. The results of this study assumed adherence to the study therapy and assumed all lipid panels collected were fasting. In addition, potential confounders, such as diet and exercise, were not accounted for; however, concomitant lipid-lowering therapy was evaluated. Three patients initiated a concomitant agent during the study period, and 6 patients discontinued a concomitant agent during the study period. Most patients were either on no concomitant lipid-lowering therapy or had concomitant therapy with no changes during the study period. Overall, it seemed that concomitant therapy likely did not have a large influence on the final results. Last, no correlations could be made between a lipid-lowering effect and tolerance and rosuvastatin dosing and frequency. This is due to the small number of patients in this study and the wide range of rosuvastatin doses and frequencies.

CONCLUSION

Non–daily-dosed rosuvastatin may be a safe and effective alternative therapy for achieving an LDL-C goal in patients with a previous statin intolerance. In addition, non–daily-dosed rosuvastatin can result in significant reductions in both TC and LDL-C. Last, pharmacist-managed patients met the NCEP LDL-C goal more often compared with other providers. ●

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Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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REFERENCES

1. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004;110(2):227-239.
2. Abd TT, Jacobson TA. Statin-induced myopathy: A review and update. *Expert Opin Drug Saf.* 2011;10(3):373-387.
3. Eckel RH. Approach to the patient who is intolerant of statin therapy. *J Clin Endocrinol Metab.* 2010;95(5):2015-2022.
4. Jacobson TA. Toward "pain-free" statin prescribing: Clinical algorithm for diagnosis and management of myalgia. *Mayo Clin Proc.* 2008;83(6):687-700.
5. McTaggart F, Buckett L, Davisdon 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.
6. Mackie BD, Satija S, Nell C, Miller J 3rd, Sperling LS. Monday, Wednesday, and Friday dosing of rosuvastatin in patients previously intolerant to statin therapy. *Am J Cardiol.* 2007;99(2):291.
7. Backes JM, Moriarty PM, Ruisinger JF, Gibson CA. Effects of once weekly rosuvastatin among patients with a prior statin intolerance. *Am J Cardiol.* 2007;100(3):554-555.
8. Gadarla M, Kearns AK, Thompson PD. Efficacy of rosuvastatin (5 mg and 10 mg) twice a week in patients intolerant to daily statins. *Am J Cardiol.* 2008;101(12):1747-1748.
9. Backes JM, Venero CV, Gibson CA, et al. Effectiveness and tolerability of every-other-day rosuvastatin dosing in patients with prior statin intolerance. *Ann Pharmacother.* 2008;42(3):341-346.
10. Ruisinger JF, Backes JM, Gibson CA, Moriarty PM. Once-a-week rosuvastatin (2.5 to 20 mg) in patients with a previous statin intolerance. *Am J Cardiol.* 2009;103(3):393-394.
11. Kennedy SP, Barnas GP, Schmidt MJ, Gilsczinski MS, Paniagua AC. Efficacy and tolerability of once-weekly rosuvastatin in patients with previous statin intolerance. *J Clin Lipidol.* 2011;5(4):308-315.
12. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285(19):2486-2497.
13. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA /ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 update: A guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation.* 2011;124(22):2458-2473.
14. U.S. Food and Drug Administration. FDA drug safety communication: Important safety label changes to cholesterol-lowering statin drugs. U.S. Food and Drug Administration Website. http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm. Updated July 3, 2012. Accessed December 20, 2013.