

Treatment Failure With Atorvastatin After Change From Rosuvastatin to Atorvastatin

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Lipid levels remained largely unchanged, and patients experienced few adverse events following the conversion of patients from rosuvastatin to atorvastatin therapy at the Huntington VAMC.

Due to the growing number of drug shortages and increasing cost of medications, large-scale formulary conversions are becoming more common and necessary for pharmacies to stay within their budget allocations. Statins are widely recognized as first-line therapy for cholesterol lowering and have been proven to reduce cardiovascular morbidity and mortality.¹⁻⁵ In addition to statin therapy, weight loss and lifestyle changes are often necessary to meet optimum low-density lipoprotein cholesterol (LDL-C) goals.⁶ According to the Adult Treatment Panel III (ATP III) guidelines, the optimum LDL-C for each patient varies based on the presence of coronary artery disease (CAD), CAD risk equivalents, and other risk factors.⁷ Patients with CAD or CAD risk equivalents have an LDL-C goal of < 100 mg/dL. Those with multiple risk factors have an LDL-C goal of < 130 mg/dL, and those with 0 to 1 risk factors have an LDL-C goal of < 160 mg/dL.^{1-3,7,8}

Numerous trials have compared

the safety and efficacy of the 3-hydroxy-3-methylglutaryl-coenzyme A inhibitors, stating that rosuvastatin 5 to 10 mg per day is equivalent to 20 mg per day of atorvastatin in terms of its ability to lower LDL-C levels.^{7,9-14} The LUNAR (Limiting Under treatment of lipids in Acute coronary syndrome with Rosuvastatin) study compared the efficacy of rosuvastatin with that of atorvastatin in decreasing LDL-C in patients with acute coronary syndrome.⁸ Rosuvastatin 40 mg was significantly more successful in lowering LDL-C and increasing high-density lipoprotein cholesterol (HDL-C) compared with atorvastatin 80-mg daily therapy.

In October 2012, the national VA Pharmacy Benefits Management (PBM) Services released guidance regarding the conversion from rosuvastatin to atorvastatin, including the dosing conversion (Table 1), stating that rosuvastatin 5 mg daily should be considered equivalent and converted to atorvastatin 20 mg daily. In general, adverse events (AEs), such as increased

liver enzymes, myopathies, and increased creatinine phosphokinase (CPK), are considered a class effect of the statins.^{13,14}

The recent 2013 American College of Cardiology/American Heart Association (ACC/AHA) Blood Cholesterol Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults has identified a large number of patients as candidates for high-intensity statins, which the authors defined as atorvastatin and rosuvastatin.⁴ These guidelines do not recommend LDL-C goals and instead use a risk calculator to determine which intensity of statin therapy is appropriate for certain patients. This change in practice will lead to a higher volume of high-intensity statin prescriptions and higher drug costs for some medical centers. Given the volume of prescriptions and the increased use of large-scale formulary conversions to reduce costs, more research is warranted to ensure equivalent dosing. With more data available and equivalent dosing defined, pharmacists may be better able to improve clinical results in patients that are included in these large-scale formulary conversions.

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METHODS

A retrospective chart review was performed on all LDL-C levels in patients receiving atorvastatin therapy due to the formulary conversion from rosuvastatin to atorvastatin at the Huntington VAMC (HVAMC) in Huntington, West Virginia, per the guidance published by the national VA PBM Services. The number of patients not at their LDL-C goal (as defined by ATP III guidelines) as a result of atorvastatin therapy was determined. Furthermore, AEs due to atorvastatin therapy such as increased liver enzymes, myopathy, and increased CPK were identified and analyzed.

The primary endpoint of this study focused on the rate of treatment failure in LDL-C reduction with atorvastatin treatment in patients previously at their LDL-C goal, as defined by the ATP III guidelines, with rosuvastatin therapy. Secondary endpoints included rate of AEs due to atorvastatin therapy, percentage in-

crease in CPK and liver enzymes as a result of atorvastatin therapy, and percentage LDL-C, HDL-C, total cholesterol (TC), and triglyceride (TGs) changes since conversion from rosuvastatin to atorvastatin.

Patients were included in the study if they were aged 18 to 89 years, previously at LDL-C goal with rosuvastatin therapy for at least 3 months, had never previously received atorvastatin, were converted to atorvastatin therapy as a result of a large-scale formulary conversion at HVAMC, and had a fasting lipid panel completed 1 to 6 months after conversion. Patients were excluded from the study if they received other lipid-lowering medications (eg, bile acid sequestrants, fibrates, niacin, or ezetimibe) in the 12 months before or after receiving statin therapy, had previously documented AEs (eg, myopathy, increased liver enzymes, increased CPK as a result of statin therapy, or history of known homozygous familial hypercholester-

Table 1. Dose Conversion

Rosuvastatin, mg/d	Atorvastatin, mg/d
5	20
10	20-40
20	40-80
40	80

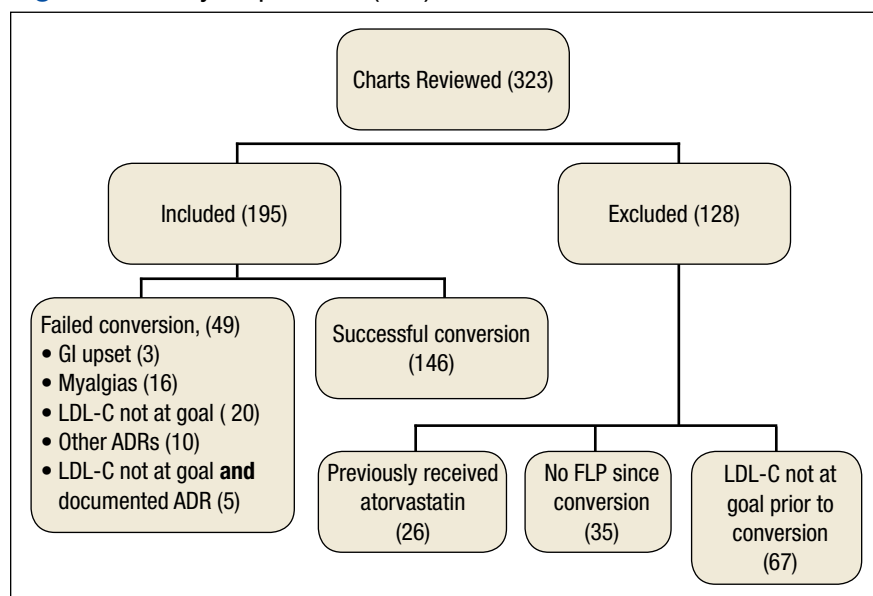
olemia) current active liver disease (ALT > 2x ULN [upper limit of normal]), unexplained CPK ≥ 3x ULN, serum creatinine (SCr) > 2 mg/dL, or history of alcohol or drug abuse within the last 5 years.

RESULTS

Three hundred twenty-three patients were identified and reviewed as converted from rosuvastatin to atorvastatin during the study period with no prior use of atorvastatin. Of the 323 charts that were reviewed, 195 patients met the study inclusion criteria and were analyzed for rate of treatment failure in terms of lipid goals and rate of AEs. Twenty of 195 patients (10.3%) were no longer at their LDL-C goal after conversion from rosuvastatin to atorvastatin. Of those 195 patients, 29 (14.9%) experienced an adverse drug reaction (ADR) as a result of atorvastatin treatment that was severe enough to result in discontinuation of the drug and switching the patient back to the originally prescribed dose of rosuvastatin. Figure 1 illustrates the number of patients and documented atorvastatin ADRs. The most common ADR documented to atorvastatin was myalgias (8.2%).

The average change in lipid levels was calculated and atorvastatin therapy was found to result in clinically insignificant changes to the lipid panel (Table 2). A 2-tailed paired t test was used to assess the statistical

Figure 1. Study Population (No.)



Abbreviations: ADRs, adverse drug reactions; FLP, fasting lipid profile; GI, gastrointestinal; LDL-C, low-density lipoprotein cholesterol.

Table 2. Changes in Lipid Panel Since Conversion to Atorvastatin (mg/dL)

	HDL-C	TC	TGs	LDL-C
Average (SD)	-4.66 (-1.06)	0.58 (9.09)	-1.97 (11.99)	-5 (-8.1)

Abbreviations: HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TGs, triglycerides.

Table 3. Changes in CPK and LFTs as a Result of Atorvastatin Therapy (IU/L)

	CPK	AST	ALT
Average (SD)	-5.88 (37.44)	-2.18 (-13.46)	1.35 (-13.78)

Abbreviations: CPK, creatinine phosphokinase; ALT, alanine aminotransferase, AST, aspartate aminotransferase; LFTs, liver function tests.

significance of these changes. Atorvastatin therapy resulted in an average decrease of LDL-C by 5.0 mg/dL ($P < .01$) in comparison to previous therapy with equivalent rosuvastatin dose. Other noted changes to lipid profile after formulary conversion included TG reduction by 2 mg/dL ($P = .69$), TC increased by 0.58 mg/dL ($P = .80$), and HDL-C reduction by 4.66 mg/dL ($P < .01$).

Although the decrease in LDL-C and HDL-C as a result of the formulary change was found to be statistically significant, they are not thought to result in a clinical difference. Clinically and statistically insignificant changes in liver enzymes and CPK were also discovered as a result of atorvastatin therapy conversion (Table 3). Atorvastatin therapy resulted in an averaged decrease of aspartate aminotransferase by 2.2 IU/L ($P = .19$) and an increase in alanine aminotransferase by 1.4 IU/L ($P = .47$). Average change in CPK was -6 IU/L ($P = .89$).

DISCUSSION

Lipid levels were found to be mostly unchanged and remained at therapy goals, demonstrating use and appropriate equivalent dosing of rosuvastatin and atorvastatin following the formulary conversion defined in Table 1. Documented ADRs were minimal, indicating the ingredient conversion was well tolerated overall by our patients. Following the release of the 2013ACC/AHA guidelines, many patients in the

VA required treatment with high-potency statins such as rosuvastatin and atorvastatin. Given the volume of statin prescriptions in the VA and the significant potential for providing the most cost-efficient lipid therapy (Table 4), the formulary conversion from rosuvastatin to atorvastatin was warranted.

Limitations

There are several limitations for extrapolating results from this study to the general population. Due to the retrospective design of the study, no formal assessment of adherence was conducted. A prospective trial, with a researcher monitoring refills and tablet counts would be more accurate to ensure patients adherence with statin therapy.

Many of the patients that were included in the formulary conversion did not have follow-up laboratory work at the time of this study and

were therefore excluded, leading to a smaller study population. A larger study population with a similar study design may be able to detect more significant correlations.

There are also several potential complications in regard to formulary conversions, including the inability to ensure the exact period that the patient switched therapies. During the conversion of rosuvastatin to atorvastatin at HVAMC, an attempt was made to minimize this confounder by converting patients on request for a refill of their rosuvastatin therapy. Last, all 185 patients that were studied were male; therefore, it is difficult to extrapolate these results for female patients.

CONCLUSIONS

This study shows that the conversion of patients from rosuvastatin therapy to atorvastatin was effective when it targeted a specific LDL-C goal

Table 4. Rosuvastatin vs Atorvastatin Cost Comparison

Rosuvastatin		Atorvastatin	
Strength, mg	Price ^a	Strength, mg	Price
5	16 x	10	x
10	11 x	20	x
20	5 x	40	x
40	5 x	80	x

^aGovernment pricing information cannot be disclosed. Difference in cost shown by using x to represent price and show how much more expensive rosuvastatin was compared with atorvastatin.

or specific reduction in LDL-C. A similar conversion would likely lead to lower drug costs for many other health systems. Additional studies will be necessary given the recent changes in the national lipid guidelines. Furthermore, studies will be needed to assess concrete clinical endpoints (cardiovascular mortality, all-cause mortality, and cardiac events). ●

Author disclosures

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

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