The Safety of Rosuvastatin as Used in Common Clinical Practice
A Postmarketing Analysis

Alawi A. Alsheikh-Ali, MD; Marietta S. Ambrose, MD; Jeffrey T. Kuvín, MD; Richard H. Karas, MD, PhD

Background—Statins are currently the mainstay of dyslipidemia management for the primary and secondary prevention of cardiovascular disease. Controversial concerns about the safety of the newly marketed statin rosuvastatin have been raised on the basis of premarketing studies and a few postmarketing reports.

Methods and Results—We reviewed rosuvastatin-associated adverse events reported to the US Food and Drug Administration over its first year of marketing. On the basis of prescription data obtained from IMS Health, rates of adverse event reports (AERs) per million prescriptions were calculated. Rates of rosuvastatin-associated AERs over its first year of marketing were compared with those seen with atorvastatin, simvastatin, and pravastatin over the concurrent timeframe and during their respective first years of marketing. Comparison was also made to the first year of marketing of cerivastatin. The primary analysis examined the composite end point of AERs of rhabdomyolysis, proteinuria, nephropathy, or renal failure. With either timeframe comparison, rosuvastatin was significantly more likely to be associated with the composite end point of rhabdomyolysis, proteinuria, nephropathy, or renal failure AERs. Reported cases of rhabdomyolysis, proteinuria, or renal failure tended to occur early after the initiation of therapy and at relatively modest doses of rosuvastatin. The increased rate of rosuvastatin-associated AERs relative to other widely used statins was also observed in secondary analyses when other categories of AERs were examined, including adverse events with serious outcomes, liver toxicity, and muscle toxicity without rhabdomyolysis.

Conclusions—The present analysis supports concerns about the relative safety of rosuvastatin at the range of doses used in common clinical practice in the general population. (Circulation. 2005;111:3051-3057.)

Key Words: cholesterol ■ complications ■ drugs ■ lipids ■ population

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) are currently the mainstay of dyslipidemia management for the primary and secondary prevention of cardiovascular disease.1 Their widespread use is driven by a robust body of evidence supporting their efficacy in preventing cardiovascular events.2 Recent data have shown that more intensive lipid lowering with high-dose statins offers additional benefit.3–6 This finding has intensified interest in more potent statins that could better achieve the more aggressive LDL cholesterol (LDL-C) targets.

Of the currently available statins, rosuvastatin has the greatest effect on LDL-C.7 Although its potency can be an advantage, controversial concerns have been raised about its safety, particularly in terms of rhabdomyolysis and renal failure, on the basis of premarketing studies and a few postmarketing reports.8–13 Given previous concerns about the safety of the potent statin cerivastatin that eventually led to its withdrawal from the global market, it is essential to assess the postmarketing safety of rosuvastatin relative to other widely used drugs in this class. Such assessment either can serve to alleviate concerns about the safety of rosuvastatin and hence encourage its appropriate use in patients who need it or can detect an adverse safety profile that was not fully appreciated in premarketing trials.14

In the present analysis, using a methodology we have previously used to assess postmarketing safety of lipid-altering drugs,15–18 we reviewed adverse event reports (AERs) to the US Food and Drug Administration (FDA) to determine the frequency of rosuvastatin-associated events relative to other commonly used statins.

Methods
Using a computer-based search engine (DrugLogic, QED Solutions), we reviewed AERs to the FDA in which rosuvastatin was listed as a suspect in causing the adverse event. The search engine includes 2 FDA databases, the Spontaneous Reporting System (1969–1997) and the Adverse Events Reporting System (1997 on), both of which...
rely on reports generated by health professionals, consumers, and manufacturers.

For comparative purposes, we evaluated 4 other statins: atorvastatin, simvastatin, pravastatin, and cerivastatin (during the time period when it was available). In doing so, we compared the postmarketing safety profile of rosuvastatin with other statins, the 3 most widely used with broadly acceptable safety profiles (atorvastatin, simvastatin, and pravastatin) and 1 with an unfavorable safety profile that eventually led to its withdrawal from the global market (cerivastatin).

Two comparative analyses were performed. For the first analysis, AERs were tabulated for the first year during which rosuvastatin was available in the United States (October 1, 2003, the first quarter after launch of rosuvastatin in the United States, to September 30, 2004, the last quarter for which data were available through the search engine) and over this concurrent time period for the other statins. This is referred to as “concurrent time period analysis.” The second approach was undertaken to control for the potential of preferential reporting of adverse events with newly marketed drugs. For the second analysis, referred to as “first year of marketing analysis,” rates of rosuvastatin-associated AERs were compared with those observed during the first year of marketing for atorvastatin (1997), simvastatin (1992), pravastatin (1992), and cerivastatin (1998).

The number of AERs to the FDA was tabulated for each of the statins. Corresponding prescription data over the time periods of interest were obtained from IMS Health for each of the statins. Corresponding prescription data over the time periods of interest were obtained from IMS Health for each of the statins.

TABLE 1. Demographic Characteristics of Individuals With AERS of Rhabdomyolysis, Proteinuria/Nephropathy, or Renal Failure (COMPOSITE AERS) Associated With Rosuvastatin, Simvastatin, Pravastatin, or Atorvastatin and Received by the US FDA Between October 1, 2003, and September 30, 2004

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin (n=145)</th>
<th>Simvastatin (n=381)</th>
<th>Pravastatin (n=52)</th>
<th>Atorvastatin (n=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriptions, in millions</td>
<td>5.2</td>
<td>29.8</td>
<td>15.0</td>
<td>72.9</td>
</tr>
<tr>
<td>Age, y</td>
<td>59.6±1.3</td>
<td>65.3±0.8†</td>
<td>66.3±1.5‡</td>
<td>62.1±0.9</td>
</tr>
<tr>
<td>Male, %</td>
<td>55</td>
<td>63</td>
<td>69</td>
<td>46</td>
</tr>
<tr>
<td>Statin dose, mg</td>
<td>16.7±1.2</td>
<td>53.1±2.8†</td>
<td>18.8±2.0</td>
<td>21.8±1.4*</td>
</tr>
<tr>
<td>Duration of therapy, d</td>
<td>69.8±7.8</td>
<td>731.3±68.4‡</td>
<td>744.7±228.7‡</td>
<td>368.8±46.0†</td>
</tr>
<tr>
<td>Other concomitant medications, n</td>
<td>4.2±0.3</td>
<td>5.0±0.4</td>
<td>6.2±0.8*</td>
<td>5.7±0.4</td>
</tr>
<tr>
<td>Outcome, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>6</td>
<td>15‡</td>
<td>10‡</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>72</td>
<td>76</td>
<td>83</td>
<td>66</td>
</tr>
<tr>
<td>No hospitalization</td>
<td>26</td>
<td>18</td>
<td>2†</td>
<td>24</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean±SE. Some reports listed both hospitalization and death as an outcome. *P<0.05, †P<0.001, ‡P<0.01 for pairwise comparison versus rosuvastatin.

**Secondary Analyses**

Comparisons pertaining to the following categories of AERS were performed as secondary analyses: (1) reports of any adverse event (ALL AERS); (2) reports of serious adverse events, defined as fatal, considered life-threatening by the reporter, or resulting in hospitalization (SERIOUS AERS); (3) reports of adverse events affecting the liver (LIVER AERS); (4) reports of adverse events affecting muscle (myalgia, myopathy, elevated creatine-phosphokinase) without frank rhabdomyolysis (MUSCLE–NO-RHABDO AERS); (5) reports of rhabdomyolysis (RHABDO AERS); (6) reports of proteinuria or nephropathy (PROTEINURIA AERS); and (7) reports of renal failure (RENAL FAILURE AERS).

**Statistical Analysis**

We used $\chi^2$ tests (with appropriate degrees of freedom) to compare rates of AERS among the various statins. For each specific adverse event category, within-group differences (ie, among all the statins examined) were first sought. If within-group differences were not statistically significant, no further analysis was undertaken for that adverse event category. If within-group differences were statistically significant, subsequent pairwise analyses were performed with $\chi^2$ tests. For all analyses, a value of $P<0.01$ was considered statistically significant to account for the multiple comparisons made. For the data in Table 1, continuous variables were compared by use of ANOVA on ranks test for within-group comparisons and the Mann-Whitney rank-sum test for pairwise comparisons to allow for unequal variance among the groups. Categorical variables were compared by use of the $\chi^2$ test. All statistical analyses were performed with SigmaStat 3.10 (Systat Software Inc).

**Results**

**Primary Analysis**

In the concurrent time period analysis, the rate of rosuvastatin-associated COMPOSITE AERs (rhabdomyolysis, proteinuria/nephropathy, or renal failure) was higher than simvastatin ($P<0.001$), pravastatin ($P<0.001$), and atorvastatin ($P<0.001$; Figure 1A). A similar pattern was observed with the first year of marketing analysis (Figure 1B). The rate of rosuvastatin-associated COMPOSITE AERs was not sig-
significantly different than simvastatin ($P=0.02$; not considered statistically significant after Bonferroni’s correction) but was significantly higher than pravastatin ($P<0.001$) and atorvastatin ($P<0.001$). Compared with what was observed with cerivastatin during its first postmarketing year, rosuvastatin-associated COMPOSITE AERs were less frequent ($P<0.001$; Figure 1B).

Demographic characteristics of individuals with COMPOSITE AERs are shown in Table 1. The reported adverse events tended to occur in relatively young individuals with no specific gender predominance and at relatively modest doses of statin. Indeed, 62% of the rosuvastatin-associated COMPOSITE AERs occurred at doses of $\leq 10$ mg/d rosuvastatin. Interestingly, the rosuvastatin-associated COMPOSITE AERs occurred early after the initiation of therapy (within the first 12 weeks) compared with the other statins. Although fatal in only a minority of cases, most COMPOSITE AERs listed hospitalization as an outcome. Table 2 lists the mean number of other concomitant medications and the percentage of COMPOSITE AERs in the concurrent time period analysis reporting concomitant use of fibrates or other drugs that can potentially interact with statins. In general, the use of such drugs was relatively rare with rosuvastatin-associated AERs and tended to be comparable to or less than what was observed with the other statins (Table 2).

Secondary Analyses: Concurrent Time Period

Figure 2 depicts the concurrent time period secondary analyses of rates of AERs from October 1, 2003, to September 30, 2004, for rosuvastatin, simvastatin, pravastatin, and atorvastatin (cerivastatin was no longer available during this time period). The rate of rosuvastatin-associated ALL AERs was higher than simvastatin, pravastatin, and atorvastatin ($P<0.001$ for each statin versus rosuvastatin; Figure 2A). Rosuvastatin-associated SERIOUS AERs, LIVER AERs, and MUSCLE–NO-RHABDO AERs were also more common than each of these AERs associated with simvastatin, pravastatin, or atorvastatin (Figure 2B, 2C, and 2D, respectively; $P<0.001$ for each statin versus rosuvastatin). Moreover, the rate of rosuvastatin-associated RHABDO AERs was higher than RHABDO AERs associated with simvastatin ($P=0.01$; Figure 2E), pravastatin, and atorvastatin ($P<0.001$ for both versus rosuvastatin; Figure 2E). Although reports of proteinuria or nephropathy associated with rosuvastatin were relatively rare (2.7 AERs per 1 million prescriptions), they were significantly more frequent than what was observed with the other statins over the concurrent time period (Figure 2F).

TABLE 2. Percent of Statin-Associated COMPOSITE AERS (of Rhabdomyolysis, Proteinuria/Nephropathy, or Renal Failure) Listing Concomitant Use of Other Drugs That Can Potentially Interact With Statins in the Concurrent Time Period Analysis From October 1, 2003, to September 30, 2004

<table>
<thead>
<tr>
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<th>Pravastatin (n=52)</th>
<th>Atorvastatin (n=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of other concomitant medications, mean±SE</td>
<td>4.2±0.3</td>
<td>5.0±0.4</td>
<td>6.2±0.8*</td>
<td>5.7±0.4</td>
</tr>
<tr>
<td>Fibric acid derivative (gemfibrozil, fenofibrate, bezafibrate), %</td>
<td>7.6</td>
<td>18.4†</td>
<td>5.8</td>
<td>5.7</td>
</tr>
<tr>
<td>Macrolide antibiotic (erythromycin, azithromycin, clarithromycin), %</td>
<td>1.4</td>
<td>5.5</td>
<td>0</td>
<td>4.1</td>
</tr>
<tr>
<td>Azole antifungal (fluconazole, itraconazole, ketoconazole), %</td>
<td>0.7</td>
<td>0.8</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>Cyclosporin, %</td>
<td>1.4</td>
<td>7.9*</td>
<td>1.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Calcium channel blocker (amlodipine, diltiazem, verapamil, nifedipine), %</td>
<td>17.2</td>
<td>25.7</td>
<td>30.8</td>
<td>30.2†</td>
</tr>
<tr>
<td>Amiodarone, %</td>
<td>2.8</td>
<td>7.3</td>
<td>3.8</td>
<td>2.9</td>
</tr>
</tbody>
</table>

*$P<0.05$, †$P<0.01$ for pairwise comparison versus rosuvastatin.
similar trend was observed with renal failure reports, in which the rate of rosuvastatin-associated RENAL FAILURE AERs was higher than simvastatin-associated RENAL FAILURE AERs, pravastatin-associated RENAL FAILURE AERs, and atorvastatin-associated RENAL FAILURE AERs ($P<0.001$ for each versus rosuvastatin; Figure 2G).

**Secondary Analyses: First Year of Marketing**

Figure 3 depicts the rates of AERs during the first postmarketing year for rosuvastatin compared with each of the other statins during their first full year of marketing, as described in Methods. Compared with rates of ALL AERs associated with other statins in the first year of marketing analysis, the difference was less marked than with the concurrent time period analysis but was still significant. The rate of rosuvastatin-associated ALL AERs was higher than simvastatin, pravastatin, atorvastatin, and cerivastatin ($P<0.001$ for each statin versus rosuvastatin; Figure 3A). For SERIOUS AERs, the rate for rosuvastatin-associated AERs was signif-
significantly lower than simvastatin ($P<0.001$) and cerivastatin ($P<0.01$) but was significantly higher than what was observed with atorvastatin or pravastatin ($P<0.001$ for both versus rosuvastatin; Figure 3B). For LIVER AERs, the rate for rosuvastatin was higher than what was observed with simvastatin, pravastatin, or atorvastatin ($P<0.05$ for simvastatin versus rosuvastatin, $P<0.001$ for pravastatin and atorvastatin versus rosuvastatin; Figure 3C) but was not significantly different from what was observed with cerivastatin during its first postmarketing year (Figure 3C). The rate of rosuvastatin-associated MUSCLE–NO-RHABDO AERs was higher than what was observed with simvastatin, pravastatin, atorvastatin, and cerivastatin ($P<0.001$ for simvastatin, pravastatin, and atorvastatin versus rosuvastatin; $P<0.01$ for cerivastatin versus rosuvastatin; Figure 3D). Rosuvastatin was also significantly more likely than simvastatin, pravasta-
tin, and atorvastatin to be associated with reports of rhabdo-
myolysis (P<0.001 for each statin versus rosuvastatin; Figure
3E). However, compared with the first year of cerivastatin,
the rate of rosuvastatin-associated RHABDO AERs was
significantly less (P<0.001; Figure 3E). The rate of
rosuvastatin-associated PROTEINURIA AERs was not sig-
nificantly different from what was observed with simvastatin,
pravastatin, and cerivastatin but was significantly higher than
what was observed with atorvastatin (P<0.001 for atorvasta-
tin versus rosuvastatin; Figure 3F). Finally, the rate of
rosuvastatin-associated RENAL FAILURE AERs was signif-
icantly greater than what was observed with pravastatin and
atorvastatin (P<0.001 for both versus rosuvastatin; Figure
3G) but was comparable to what was observed with simva-
statin and tended to be lower than what was observed with
cerivastatin (P=0.054; Figure 3G).

**Discussion**

We reviewed rosuvastatin-associated adverse events reported
to the US FDA over its first year of marketing and compared
the rates of such events with other statins over the concurrent
time frame and during their respective first year of marketing.
We observed that with either comparison, rosuvastatin was
several-fold more likely to be associated with the composite
end point of rhabdomyolysis, proteinuria, nephropathy, or
renal failure AERs. The increased rate of rosuvastatin-
associated AERs relative to the 3 most widely used statins in
the United States was also observed when other categories of
AERs were examined, including serious adverse events and
reports of liver toxicity, as well as muscle toxicity without
rhabdomyolysis. There were a few exceptions in which this
trend was not observed, such as the lower rate of serious
AERs and a comparable rate of renal failure reports with
rosuvastatin relative to the first year of marketing of simva-
statin, as well as a relatively low incidence of proteinuria and
nephropathy reports, comparable to what was observed dur-
ing the first postmarketing year of simvastatin and pravasta-
tin. We also observed that compared with first year of
marketing of cerivastatin, the rate of rosuvastatin-associated
liver injury reports was not significantly different.

The approach we used in the present analysis takes advantage of the “real-life” population exposure captured in
the FDA AERs system. This overcomes the limitation of
trolled premarking trials, which typically exclude pa-
ten who may be predisposed to a certain adverse event but
who nonetheless are likely to receive the drug after it is
marketed. In addition, premarking trials aimed at safety or
efficacy assessment are often underpowered to detect rela-
tively rare adverse events. Hence, postmarketing assessments
such as the one presented here are helpful in attempts to
identify safety concerns that can potentially be missed early
on.

On the other hand, the findings we report should be interpreted within the context of the intrinsic limitations of
postmarketing adverse event analyses. The data used reflect
adverse event reporting rates, not actual adverse event rates.
In clinical practice, adverse events tend to be underreported,
and serious events are more likely to be reported than milder
ones. Hence, the rates presented here are likely underesti-
mates of true adverse events with possible relative overrep-
resentation of serious events. Moreover, the retrospective
nature of the analysis does not allow confirmation of causal-
ity or control of potential confounders.

One potential confounder is the time period studied relative
to the life cycle of a drug, because providers tend to
preferentially report adverse events associated with newly
marketed drugs. In addition, certain adverse events may not
be recognized as related to a particular class of drugs until
later. For example, the very low rates of simvastatin- and
pravastatin-associated RHABDO AERs during their first
postmarketing year (1992) may be the result of underrecog-
nition of this statin-related adverse event in an era predating
the large landmark statin trials and the subsequent widespread
use of these drugs. Postmarketing analyses can also be
influenced by the publicity, favorable or otherwise, surround-
ing the drug of interest. Hence, it is conceivable that some of
the negative publicity surrounding the safety profile of
rosuvastatin and the accompanying heightened public aware-
ness contributed to the increased rates of reported
rosuvastatin-associated adverse events. The extent to which
that publicity contributed to our findings is uncertain. Other
time-dependent variables can potentially affect the assess-
ment of postmarketing safety. For example, the relatively low
rate of atorvastatin-associated AERs during its first year of
marketing could be partially related to the availability of only
the 10-mg dose during the first year, hence ameliorating the
preferential reporting often seen early after the release of a
new drug. Therefore, in an effort to account for possible
time-dependent effects, we present comparisons of
rosuvastatin-associated AERs during its first year of market-
ing with the other statins over the concurrent time frame and
during the respective first year of marketing of each statin.
Although the first year of marketing analysis is limited by the
use of two different time points, it has the advantage of using
similar phases of the life cycle of each drug.

An additional limitation of our findings is the lack of
insight into the mechanism(s) that resulted in the higher rate
of AERs with rosuvastatin. For example, it remains unclear
whether the observed rate of rosuvastatin-associated AERs is
due in part to its greater LDL-C-lowering effect compared
with the other statins. If this were the case, then the rates of
AERs with the other statins might also be higher if used at
equivalent LDL-lowering doses. Despite this important ca-
veat, however, our findings remain clinically relevant be-
cause they reflect the AERs observed with each statin as it is
commonly used in clinical practice. Similarly, we are unable
to provide insight about any potential role of the distinct
chemical structure of each statin or of differences in metab-
olism or dose response.

In conclusion, this comparative postmarketing analysis of
rosuvastatin-associated adverse events reported to the US
FDA raises concerns about the safety of this drug at the range
of doses used in common clinical practice in the general
population. The occurrence of rhabdomyolysis and renal
toxicity relatively early after initiation of therapy (within the
first 12 weeks on average), suggests that vigilant surveill-
ance for adverse effects during initiation of therapy may help
ameliorate the risk of toxicity when rosuvastatin is used.
Healthcare providers and regulatory agencies will have to carefully consider the findings of this postmarketing analysis, along with safety analyses from clinical trials, to determine the extent to which the observed increased rates of AERs with rosvuastatin offset the potential benefit of its greater potency for LDL-C reduction. It would seem prudent at the current time for healthcare providers to consider other statins as first-line therapy, to initiate therapy in appropriate patients at lower doses, to consider combination LDL-C–lowering therapy (eg, statin combined with ezetimibe), and to vigilantly monitor for adverse events if rosvuastatin is used.

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Dr Karas was an Established Investigator of the American Heart Association during the period when this work was performed. We are grateful to Dr Inga Peter for consultation with regard to the statistical analyses.

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References
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