Safety and Tolerability of Pravastatin in Long-Term Clinical Trials
Prospective Pravastatin Pooling (PPP) Project

Marc A. Pfeffer, MD, PhD; Anthony Keech, MD; Frank M. Sacks, MD; Stuart M. Cobbe, MD; Andrew Tonkin, MD; Robert P. Byington, PhD; Barry R. Davis, MD, PhD; Carola P. Friedman, MD; Eugene Braunwald, MD

Background—Therapeutic decisions regarding pharmacological therapy should be based on safety and tolerability as well as efficacy data. Clinical trials designed to assess efficacy are often insufficiently powered to generate reliable safety data.

Methods and Results—The West of Scotland Coronary Prevention Study (WOSCOPS), the Cholesterol and Recurrent Events (CARE), and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) studies collectively accumulated >112 000 person-years of exposure in double-blind randomized trials comparing placebo and pravastatin (40 mg once daily). During 5 years of exposure, the incidence of fatal and nonfatal cancers was similar between pravastatin and placebo groups. No differences in noncardiovascular serious adverse events were detected. With >243 000 blood sample analyses, the percentage of patients with any abnormal liver function test after baseline sampling was similar (>3× the upper limit of normal for alanine aminotransferase: 128 [1.4%] versus 131 [1.4%] patients for pravastatin versus placebo, respectively). Study medication was withdrawn in 3 pravastatin and 7 placebo patients due to creatine phosphokinase elevations; no cases of mild or severe myopathy were reported. A Cox regression model considering treatment group, age, diabetes, smoking, whether primary or secondary prevention study, and cardiovascular serious adverse events indicates that the likelihood of discontinuing pravastatin was less than placebo.

Conclusions—This prospective analysis indicates that during prolonged exposure, 40 mg of pravastatin is well tolerated, with no excess of noncardiovascular serious adverse events, including liver function abnormalities and laboratory and clinical evidence for myositis. These extensive safety and tolerability data provide important information for therapeutic decisions regarding this pharmacological agent. (Circulation. 2002;105:2341-2346.)

Key Words: statins ■ pravastatin ■ safety ■ rhabdomyolysis ■ myositis

Reductions in the prevalence and severity of cardiovascular risk factors have been prominent contributors toward the decline in cardiovascular morbidity and mortality observed in the last several decades.1,2 Favorable lifestyle modifications such as avoidance of smoking, weight reduction, dietary modifications, and increasing physical activity are based on sound epidemiological data and raise no safety concerns. However, a strategy that uses long-term pharmacological therapy for cholesterol lowering as well as for other risk factors, such as hypertension, should be based on definitive data concerning efficacy and the safety and tolerability of the therapy to derive a rational risk-benefit assessment. In many respects, safety and tolerability are as important as efficacy in defining the clinical thresholds to initiate long-term pharmacological therapy to modify a risk factor.

Large scale, well-conducted, placebo-controlled, randomized clinical trials have established conclusive evidence that the long-term use of certain 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) results in important reductions in the risk of experiencing major cardiovascular events in patients with a wide range of lipid levels, both with3–6 and without7,8 a history of heart disease. These major clinical trials were designed with sufficient statistical power to detect the efficacy of the particular statin in reducing...
predefined cardiovascular events. However, individually, these studies generally do not provide sufficient exposure to uncover relatively uncommon safety issues. Indeed, before these studies, the safety of earlier pharmacological strategies to lower cholesterol had been questioned when nonsignificant increases in noncardiovascular deaths were reported with cholestyramine and gemfibrozil therapy in some studies. Rodent toxicity data raised questions concerning the possible carcinogenesis of lipid-lowering agents. Because statins inhibit a major liver enzyme, hepatic safety has been an ongoing concern. Marked elevations in plasma levels of certain statins metabolized by CYP3A4 have been experienced with coadministration of other agents that inhibit this pathway. Indeed, reports of rhabdomyolysis with the coadministration of mibefradil and statins sharing this metabolic pathway led to the withdrawal of this antihypertensive agent. The recent worldwide withdrawal of cerivastatin as a consequence of postmarketing reports of a relatively high rate of fatal rhabdomyolysis has appropriately heightened concerns about the use of statins.

The investigators from the West Of Scotland Coronary Prevention Study (WOSCOPS), the Cholesterol And Recurrent Events (CARE) study, and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study formed the Prospective Pravastatin Pooling (PPP) project to combine the cumulative experience of their 3 major long-term, large, placebo-controlled trials of a single dose of pravastatin. The objective was to prospectively and cooperatively pool data to derive more precise quantitative estimates of the efficacy of pravastatin in predefined subgroups, for less common events such as stroke, and to evaluate potential safety issues. Collectively, these 3 studies amassed >112 000 person-years of experience comparing pravastatin (40 mg once daily) with placebo in a rigorous double-blind manner. This report describes the tolerability and safety analyses of the PPP project.

Methods

The protocol for the PPP collaboration has been described previously, as have the major subgroup, stroke analyses, and mortality data. The individual data sets from these 3 large double-blind trials were combined for statistical analysis. Previous PPP analyses were based on the intent-to-treat principle, including all 19 768 patients randomized into any of the 3 trials. This prespecified safety analysis includes the 19 592 patients who received at least one dose of blinded study medication (n=9809 for pravastatin; n=9783 for placebo) and excludes 176 patients (≤1%) who were not exposed to study medication. The duration of exposure to study drug was calculated from the day of the first dose to the last day taken, without adjustments for temporary treatment interruptions.

Safety Analysis

Safety was evaluated by multiple analyses using the frequency of all reported fatal and nonfatal serious adverse events. A serious adverse event was defined as an adverse event that was fatal, immediately life-threatening, permanently disabling, a congenital anomaly, cancer, an overdose, or that required overnight or prolonged hospitalization. Fatal events, whether cardiovascular or noncardiovascular, were previously described for the PPP cohort. To analyze cancers, the incidence of primary malignancies reported during and within 30 days after study completion was compared.

Results

Demographics and baseline characteristics of the 19 592 patients in the safety analysis of the PPP were very similar to those previously reported in the overall PPP cohort. Of the 19 592 patients, 13 173 were enrolled in either CARE or LIPID (secondary prevention studies) and 6419 patients were enrolled in WOSCOPS (primary prevention study). The median age of the overall population was 59 years, with a maximum of 75 years at the time of study drug initiation. Approximately 25% of the population was ≥65 years at randomization. The overall population was 89% male and 11% female (WOSCOPS was confined to men). The mean exposure to study medication was >4.5 years, with a median of 5 years and a maximum duration of 7.1 years (Table 1).
Deaths and Cancer

Fewer pravastatin-treated patients died. This was due to a reduction in cardiovascular deaths in those assigned to pravastatin (n = 11005/394) compared with placebo (n = 11005/502; P = 0.001), with no difference observed in noncardiovascular deaths. There was no category of noncardiovascular death in which the proportion of deaths differed between the pravastatin and placebo-assigned groups. Fatal primary cancers occurred in 455 of the 19,592 (2.3%) patients, with no differences between treatment groups in these relatively infrequent events. Adding the incidence of nonfatal cancers increased the number of patients in whom at least one primary cancer was diagnosed to 9.5% of the population (1860 of 19,592; Table 2). There were no differences between the pravastatin and placebo groups for any primary cancer as categorized by body system, except in musculoskeletal/connective tissue, which were composites of different histological types and anatomic sites with no pattern according to treatment assignment.

The incidence of breast cancer was 0.2% (n = 22) in the pravastatin-treated group and 0.1% (n = 11) in those assigned to placebo (P = 0.080). An imbalance in breast cancer had previously been noted in the CARE study.5 The LIPID study, compared with CARE, enrolled a larger number of women: 756 were in the pravastatin-treated group and 760 were in the placebo-treated group. In the LIPID study, there were 10 reports (1.3%) of breast cancer in pravastatin-treated women and 8 reports (1.1%) in placebo-treated women. In addition, 2 cases of breast cancer were reported in men; both were assigned placebo.

Serious Adverse Events

Reports of serious adverse events related to the cardiovascular system were less frequent in the pravastatin-treated group.

Safety

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Hepatic Safety

There was no difference in serious adverse events related to the hepatobiliary system between the pravastatin (n = 255; 2.6%) and the placebo-treated subjects (n = 297; 3.0%). The most common reported serious adverse event related to the hepatobiliary system was gallbladder disorders, which was reported in 186 (1.9%) of pravastatin-treated and 208 (2.1%) of placebo patients. The incidence of any abnormality of ALT after baseline was similar between the pravastatin and the

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**Table 1. Total Extent of Exposure to Study Medication**

<table>
<thead>
<tr>
<th>Extent of exposure to study medication</th>
<th>40 mg of Pravastatin (n = 9809)</th>
<th>Placebo (n = 9783)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD, y</td>
<td>4.6 ± 1.7</td>
<td>4.5 ± 1.8</td>
</tr>
<tr>
<td>Median, y</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Minimum, d</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Maximum, y</td>
<td>7.1</td>
<td>7.1</td>
</tr>
</tbody>
</table>

**Table 2. Primary Cancer: Incidence by Body System**

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<table>
<thead>
<tr>
<th>Body System</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pravastatin, n (%)</td>
</tr>
<tr>
<td>Total number of subjects with at least one primary cancer adverse event†</td>
<td>946 (9.6)</td>
</tr>
<tr>
<td>Dermatological</td>
<td>357 (3.6)</td>
</tr>
<tr>
<td>Endocrine/metabolic/electrolyte imbalance</td>
<td>24 (0.2)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>137 (1.4)</td>
</tr>
<tr>
<td>General</td>
<td>16 (0.2)</td>
</tr>
<tr>
<td>Hematopoietic</td>
<td>38 (0.4)</td>
</tr>
<tr>
<td>Hepatic/biliary</td>
<td>10 (0.1)</td>
</tr>
<tr>
<td>Musculoskeletal/connective tissue</td>
<td>9 (&lt;0.1)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>16 (0.2)</td>
</tr>
<tr>
<td>Renal/genitourinary</td>
<td>266 (2.7)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>122 (1.2)</td>
</tr>
<tr>
<td>Special senses</td>
<td>4 (&lt;0.1)</td>
</tr>
</tbody>
</table>

*Difference of incidence.
†A total of 48 pravastatin and 107 placebo-treated patients had >1 body system cancer; ‡including breast.

There were no differences in the number of serious adverse events reported for noncardiovascular reasons (Figure 1).

**Figure 1. Most common serious adverse events, excluding cardiovascular events. GI indicates gastrointestinal.**
The risk of exacerbating an already existing liver function abnormality was evaluated by a subgroup analysis of the 579 patients who were randomized with an abnormal ALT value. At baseline, 317 (3.2%) of the pravastatin-treated subjects and 262 (2.6%) of the placebo-treated subjects had ALT elevations that exceeded baseline (between 1 and 3 × ULN). The number of these patients who subsequently showed an increase that was between 1.5 and 3 × ULN was comparable (127 of 317 [40.1%] versus 101 of 262 [38.5%] for pravastatin and placebo, respectively). Importantly, the number of these patients with baseline abnormalities in whom ALT was subsequently >3 × ULN on any postrandomization sample was 16 of 317 (5.0%) in the pravastatin-treated subjects versus 19 of 262 (7.3%) for placebo-treated subjects.

**Musculoskeletal Safety**
There were no cases of myopathy, which was defined as muscle aching or muscle weakness in conjunction with increases of CPK >10 × ULN, or confirmed cases of rhabdomyolysis reported for either pravastatin or placebo-treated groups. The incidence of adverse events due to myalgia and/or myositis was comparable between treatment groups. Although women reported myalgia and myositis more frequently than men, there was no treatment effect. No differences were observed between older versus young subjects. Postbaseline abnormalities of CPK occurred with similar frequencies in the placebo- and pravastatin-treated groups (Table 3).

**Renal Safety**
Renal failure or chronic renal failure was designated as a serious adverse event in 78 of 9783 (0.79%) placebo and 48 of 9809 (0.49%) pravastatin subjects. Although more detailed evaluations were not conducted, there was at least no suggestion of drug-induced severe renal problems.

**Tolerability**
Discontinuation of the blinded study medication for any reason was less frequent in the pravastatin than in the placebo group (2217 of 9809 [22.6%] versus 2728 of 9783 [27.8%] for pravastatin versus placebo, respectively; *P*<0.001; Figure 2). An analysis of reported adverse experiences leading to drug discontinuation by body system did not reveal any increase in discontinuation rate attributed to pravastatin therapy for any body system. Indeed, patients taking placebo were more likely to discontinue due to an adverse event classified as related to the cardiovascular, endocrine/metabolic, and general body systems. Therefore, an additional exploratory analysis that excluded patients who discontinued medication after a cardiovascular event still indicated that discontinuation of the blinded study medication was less frequent in the pravastatin than in the placebo group (2050 of 9642 [21.3%] versus 2451 of 9506 [25.8%] for pravastatin versus placebo, respectively; *P*<0.001).

The likelihood of discontinuing study medication was analyzed with a Cox proportional hazards model, which in addition to treatment group used covariates of age, enrollment in either the primary or secondary prevention studies, history of diabetes, smoking status, presence of a serious adverse event attributed to the cardiovascular body system, and treatment by primary or secondary prevention study interaction. Despite the attempts to adjust for potential confounders for long-term continuation on study medication, assignment to pravastatin remained a significant determinant of reduced likelihood to discontinue study medication (increased tolerability; Table 4). Individuals with a history of diabetes, smokers, and those in the primary prevention study were more likely to discontinue study medication, whereas those

### Table 3. Serum Chemistry Abnormalities

<table>
<thead>
<tr>
<th></th>
<th>ALT Abnormalities</th>
<th>CPK Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pravastatin</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>40 mg (n=9185), n (%)</td>
<td>40 mg (n=5245), n (%)</td>
</tr>
<tr>
<td>Any value &gt;1.5×ULN</td>
<td>804 (8.8)</td>
<td>746 (8.2)</td>
</tr>
<tr>
<td>&gt;1.5×ULN to ≤3×ULN</td>
<td>676 (7.4)</td>
<td>615 (6.7)</td>
</tr>
<tr>
<td>&gt;3×ULN to ≤5×ULN</td>
<td>84 (0.9)</td>
<td>90 (1.0)</td>
</tr>
<tr>
<td>&gt;5×ULN to ≤7×ULN</td>
<td>24 (0.3)</td>
<td>19 (0.2)</td>
</tr>
<tr>
<td>&gt;7×ULN to ≤9×ULN</td>
<td>6 (&lt;0.1)</td>
<td>9 (&lt;0.1)</td>
</tr>
<tr>
<td>&gt;9×ULN</td>
<td>14 (0.2)</td>
<td>13 (0.1)</td>
</tr>
</tbody>
</table>

ULN = upper limit of normal.
TABLE 4. Factors Affecting Discontinuation of Study Medication: Results From the Multivariate Cox Regression Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group (pravastatin)</td>
<td>0.69</td>
<td>0.64, 0.74</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>1.00, 1.01</td>
<td>0.471</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.83</td>
<td>0.76, 0.91</td>
<td>0.001</td>
</tr>
<tr>
<td>Primary/secondary prevention</td>
<td>1.15</td>
<td>1.04, 1.26</td>
<td>0.004</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>1.34</td>
<td>1.21, 1.49</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking status</td>
<td>1.25</td>
<td>1.16, 1.36</td>
<td>0.001</td>
</tr>
<tr>
<td>Presence of a serious adverse event in CV system*</td>
<td>0.76</td>
<td>0.71, 0.81</td>
<td>0.001</td>
</tr>
<tr>
<td>Treatment by primary/secondary prevention interaction</td>
<td>1.40</td>
<td>1.24, 1.57</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Time-dependent covariate.

experiencing a serious adverse cardiovascular event or who were men were more likely to continue their assigned medication. Independent of these and other factors, assignment to pravastatin was associated with a higher likelihood of continuing study medication (Table 4).

Discussion

The safety of a pharmaceutical agent is a relative term. Safety concerns for agents used long-term in the treatment of relatively well individuals as preventive therapies would differ from those for agents used for the treatment of life-threatening illnesses for shorter durations. Statins are generally used for long-term exposure. Indeed, even in a secondary prevention study such as LIPID, which enrolled relatively well individuals as preventive therapies would have a much closer surveillance than those in general practice. Trial protocols require frequent visits and, depending on the study, surveillance laboratory evaluations. As a result, in the combined PPP experience, ∼243 000 blood samples were obtained and analyzed. On the basis of this extensive experience, we were able to quantify that the risk of developing elevations in hepatic transaminase levels while taking pravastatin (40 mg once daily) was no greater than placebo. Similarly, in the Air Force/Texas Coronary Atherosclerosis Prevention Study, the frequency of detection of consecutive 3×ULN elevations in hepatic transaminase was not significantly increased with lovastatin compared with placebo.

In the Scandinavian Simvastatin Survival Study, the finding of any 3×ULN value of ALT during frequent surveillance was slightly higher in the simvastatin group compared with placebo. However, there was no difference in the groups with respect to the number of patients who had therapy discontinued because of elevated hepatic enzymes (8 of 2221 simvastatin patients and 5 of 2223 placebo patients).

The recent report of the Heart Protection Study, which has >20 000 patients (10 269 on simvastatin and 10 267 on placebo) who were followed for ∼5 years, reported ALT >3×ULN in only 77 (0.8%) of the patients assigned the statin and 65 (0.6%) of those assigned placebo.

Similarly, despite pre-study concerns about statin-induced myotoxicity, increased rates of rhabdomyolysis or creatinine kinase >10×ULN were not detected in these large-scale clinical trials of first-generation statins (lovastatin, pravastatin, and simvastatin).

As a result of major clinical trials with >100 000 patient-years of exposure, a reliable safety profile of these well-studied agents was available.

With the administration of any pharmacological compound, safety must always be a consideration. Acquisition of safety data is a continuous process that should never be considered complete. At this time, our extensive pooled data set had a 99% chance of detecting events that had a frequency >1 in 1000 and a 62.5% chance for events with a frequency of ≥1 in 10 000 during the period of monitoring. The postmarketing detection of an excessive risk of fatal rhabdomyolysis associated with cerivastatin serves to reinforce the need for specific safety information for each molecule. Because this particular agent was not used in long-term morbidity/mortality trials, the available safety information was much less robust. Although differences in lipophilicity, drug metabolism by the hepatic cytochrome P-450 system, and drug interactions have been postulated to explain the different safety profiles of statins, there should be no substitute for quantitative safety assessments such as from controlled, exposure agent–specific safety data.

Statins decrease intracellular cholesterol production in the liver by partial inhibition of this rate-limiting enzyme for cholesterol biosynthesis. As such, the potential for hepatic toxicity has been a concern since their early development, as has their potential to produce myopathy and rhabdomyolysis. Given these concerns about skeletal muscle and liver function abnormalities, relevant assays for safety surveillance were incorporated into the protocols of these large-scale trials. Indeed, in many respects, patients in clinical trials generally have much closer surveillance than those in general practice.

ULN value of ALT during frequent surveillance was considered complete. At this time, our extensive pooled data had a 99% chance of detecting events that had a frequency >1 in 1000 and a 62.5% chance for events with a frequency of ≥1 in 10 000 during the period of monitoring. The postmarketing detection of an excessive risk of fatal rhabdomyolysis associated with cerivastatin serves to reinforce the need for specific safety information for each molecule. Because this particular agent was not used in long-term morbidity/mortality trials, the available safety information was much less robust. Although differences in lipophilicity, drug metabolism by the hepatic cytochrome P-450 system, and drug interactions have been postulated to explain the different safety profiles of statins, there should be no substitute for quantitative safety assessments such as from controlled, exposure agent–specific safety data.
The PPP experience is extensive, comprising >112,000 person years, and provides quantitative data on the safety and tolerability of pravastatin during a median 5-year period in subjects both with and without known heart disease, with elevated and average baseline LDL cholesterol levels. The risk of experiencing noncardiovascular adverse events in the groups randomized to 40 mg of pravastatin was no greater than that observed in the placebo groups. The specific concerns about myopathy and hepatic liver enzyme abnormalities during pravastatin therapy were not confirmed. Although the reason for administering pharmacological therapy must be based on efficacy data, the threshold at which one does choose an agent must also carefully consider quantitative safety data. In the PPP experience, the clinical efficacy of 40 mg of pravastatin was associated with a safety and tolerability profile similar to placebo.

Acknowledgment
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References
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