Rosiglitazone and Delayed Onset of Proliferative Diabetic Retinopathy

Lucy Q. Shen, MD; Angie Child, MD; Griffin M. Weber, MD, PhD; Judah Folkman, MD†; Lloyd Paul Aiello, MD, PhD

Objective: To evaluate whether rosiglitazone maleate, an oral peroxisome-proliferating activated receptor γ agonist and oral insulin sensitizing agent with potential antiangiogenic activity, delays onset of proliferative diabetic retinopathy (PDR).

Methods: Longitudinal medical record review of all patients treated with rosiglitazone receiving both medical and ophthalmic care at the Joslin Diabetes Center from May 1, 2002, to May 31, 2003 (N = 124), and matched control patients not taking a glitazone drug (N = 158). The mean duration of follow-up was 2.8 years (range, 0.3-9.0 years).

Results: Baseline characteristics and final hemoglobin A₁c values (7.6% and 7.8%, respectively) were similar in the rosiglitazone and control groups (P = .10). In eyes with severe nonproliferative diabetic retinopathy at baseline (rosiglitazone group, 14 eyes; control group, 24 eyes), progression to PDR over 3 years occurred in 19.2% in the rosiglitazone group and 47.4% in the control group, representing a 59% relative risk reduction (Wilcoxon, P = .045; log-rank, P = .059). Fewer eyes in the rosiglitazone group experienced 3 or more lines of visual acuity loss (P = .03). The incidence of diabetic macular edema was similar in both groups.

Conclusions: Rosiglitazone may delay the onset of PDR, possibly because of its antiangiogenic activity. Future clinical investigations should consider analysis of this potential benefit along with ongoing evaluation of potential cardiac risk in studies where the risk-benefit profiles are deemed appropriate.

## METHODS

The study was initiated in 2003 and approved by the Joslin Diabetes Center Institutional Review Board. Patients fulfilled the following criteria: prescribed rosiglitazone by May 31, 2003, received care at both the Joslin and its affiliated Beetham Eye Institute (BEI), and at least one ophthalmic examination at the BEI between May 1, 2002, and May 31, 2003. A control group matched for baseline characteristics and follow-up duration was identified after systemic data from the treatment group were collected. Other selection criteria were the same as for the treatment group, except that control patients had no history of receiving prescriptions for rosiglitazone, pioglitazone hydrochloride, or troglitazone. Data were collected using standardized forms from the Joslin medical records. Systemic data included demographic information, factors affecting progression of diabetic retinopathy (DR) or angiogenesis, and adverse effects associated with rosiglitazone. For this study, type 1 diabetes mellitus was defined as diagnosis of diabetes before age 30 years, whereas type 2 diabetes mellitus was defined as diagnosis at 30 years or older.

Ophthalmic data included visual acuity, clinical DR severity and diabetic macular edema (DME) severity, and treatment of DR and DME. All visual acuity measurements were best-corrected and conducted on Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts. Severity of DR and DME were graded by all ophthalmologists at the BEI according to ETDRS clinical guidelines. Individual ophthalmologists were unaware that a particular patient was included in the study at the time of evaluation. Previous studies had shown that the consistency of BEI ophthalmologist grading of DR was comparable to the interreader results of the ETDRS study and to masked evaluation of ETDRS standardized photographs. Clinical photographs, when available, were used to confirm clinical DR grading.

## RESULTS

The primary study end point was the development of PDR in patients with nonproliferative diabetic retinopathy (NPDR) at baseline. Secondary end points included 3 or more lines worsening of visual acuity on the ETDRS chart (moderate visual loss), evidence of PDR progression in patients with PDR at baseline, and the development of clinically significant macular edema (CSME) in patients with no history of macular edema at baseline.

### BASELINE CHARACTERISTICS

Comparisons of means between the rosiglitazone and control groups were performed using a 2-sample t test for populations with normal distribution. Categorical data expressed in percentages were compared using a chi-squared test. When the expected frequencies were excessively small, Fisher exact tests were performed. Analysis of ophthalmic data excluded information from patients who underwent only 1 ophthalmic evaluation during the study period. Survival analysis using the Kaplan-Meier method was used to compare data on cumulative rates with various follow-up times and eyes as a unit. Differences between survival curves of the 2 groups were assessed with both Wilcoxon and log-rank tests. Cumulative percentages were obtained from survival curves at 6 months and annually for up to 6 years of follow-up. 

## STATISTICAL ANALYSIS

We evaluated 124 rosiglitazone-treated patients and 158 control patients with a mean follow-up period of 2.7 and 2.9 years, respectively. Baseline characteristics were well matched (Table 1). Overall, patients were predominantly white and had type 2 diabetes mellitus; 42.7% of rosiglitazone-treated patients and 42.4% of control patients were women. The mean age of participants in the rosiglitazone group was 62 years and in the control group 64.2 years, with 15.4 and 16.9 years since diagnosis of diabetes, and hemoglobin A1c (HbA1c) values of 8.4% and 8.1%, respectively. Patients with type 2 diabetes mellitus aged 30 to 45 years represented 36% of the treatment group, 35% of the control group, and 31% of all study participants.

### Table 1. Baseline Characteristics and Systemic Data

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone Group</th>
<th>Control Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>62.4 (11.9)</td>
<td>64.2 (11.3)</td>
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<tr>
<td>Male sex, %</td>
<td>57.3</td>
<td>57.6</td>
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<td>White race, %</td>
<td>84.7</td>
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<td>Type 2 diabetes mellitus, %</td>
<td>95.0</td>
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<td>.64</td>
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<td>Duration of diabetes, mean, SD</td>
<td>15.4 (7.8)</td>
<td>16.9 (8.8)</td>
<td>.13</td>
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<tr>
<td>Length of follow-up, mean (SD), y</td>
<td>2.7 (1.9)</td>
<td>2.9 (1.5)</td>
<td>.40</td>
</tr>
<tr>
<td>HbA1c value, mean (SD), %</td>
<td>8.4 (1.7)</td>
<td>8.1 (1.4)</td>
<td>.14</td>
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<tr>
<td>Final</td>
<td>7.6 (1.4)</td>
<td>7.8 (1.3)</td>
<td>.10</td>
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<td>Blood pressure, mean (SD), mm Hg</td>
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<tr>
<td></td>
<td>Final</td>
<td>132/71 (14/9)</td>
<td>.81/23</td>
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<td>Baseline visual acuity, mean, OD</td>
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<td>20/25</td>
<td>.22</td>
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<td>Baseline visual acuity, mean, OS</td>
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<td>20/25</td>
<td>.71</td>
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<td>Pedal edema, %</td>
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<td>Anemia, %</td>
<td>10.8</td>
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<td>.10</td>
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<td>Abnormal LFT results, %</td>
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<td>BMI, mean (SD)/No. of patients</td>
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<td>32.1 (6.6)/143</td>
<td>.501</td>
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<td>Microalbuminuria, %</td>
<td>52.4</td>
<td>67.7</td>
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<td>Proteinuria, %</td>
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<td>Use of insulin, %</td>
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<td>Use of celecoxib, %</td>
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<td>History of primary cancer, %</td>
<td>8.1</td>
<td>12.7</td>
<td>.21</td>
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<tr>
<td>History of metastatic cancer, %</td>
<td>0.8</td>
<td>0</td>
<td>.44</td>
</tr>
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</table>

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HbA1c, hemoglobin A1c; LFT, liver function test.

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baseline systolic and diastolic blood pressures and mean visual acuity (20/25 in each group) were also similar. Because of medical record policies in effect during the study period, information about ethnicity was available for only 72 patients (58.1%) in the rosiglitazone group and 107 in the control group (67.7%). The percentages of white patients in the 2 groups (rosiglitazone, 84.7%; and control, 73.8%) were not statistically different (P = .08), and the distribution of nonwhite ethnicities was not assessed.

SYSTEMIC FACTORS

Glycemic control, as measured by the last available HbA1c value, improved comparably in both groups by the end of the study (rosiglitazone, 7.6%; and control, 7.8%; P = .10) (Table 1). Known adverse effects of rosiglitazone, including pedal edema, anemia, abnormal liver function tests, and congestive heart failure, were more frequent in the rosiglitazone group, but none of these differences were statistically significant.

A variety of factors that might affect DR progression or angiogenesis were also assessed (Table 1). Duration was often unavailable for these factors, and thus the analysis was not adjusted for follow-up time. Body mass index (BMI) data (calculated as weight in kilograms divided by height in meters squared) were available for 89.5% of patients in the study. Other angiogenesis-related factors, such as presence of primary or metastatic malignant neoplasms, and celecoxib use were also equivalent.

PROGRESSION TO PDR

Distribution of baseline NPDR severity is shown in Table 2. Severe NPDR was found in 14 eyes (6.4%) in the rosiglitazone group and in 24 eyes (9.3%) in the control group at baseline. Progression to PDR by severity of NPDR at baseline is shown in Figure 1. Within 1 year, PDR developed in 7.7% and 29.2% of the rosiglitazone and control groups, respectively (Figure 1A). At 3 years’ follow-up, PDR was found in 19.2% and 47.4% of patients, respectively, representing a 59.5% relative risk reduction in the rosiglitazone group. When accounting for lost to follow-up and follow-up duration, this difference was statistically significant by the Wilcoxon method (P = .045) and neared significance by log-rank method (P = .059). In patients with moderate or mild NPDR at baseline (Figure 1B and C), no significant differences were observed over 3 years. None of the patients without DR at baseline developed PDR during the study. The number of eyes in each group at each follow-up time is indicated in Figure 1 and Figure 2.

If the antiangiogenic actions of rosiglitazone predominantly accounted for the delayed onset of PDR, then prevention of the severe NPDR to PDR transition would be expected, rather than a reduction of NPDR progression. Thus, we evaluated progression to PDR in patients with moderate NPDR at baseline who subsequently developed severe NPDR during follow-up (Figure 1D). In this subgroup, 3 years after the diagnosis of severe NPDR, 11.1% of patients in the rosiglitazone group and 31.8% in the control group developed PDR, representing a 65.1% relative risk reduction (Wilcoxon, P = .12; log-rank, P = .17). Rosiglitazone dosing regimens (4 mg/d, 4 mg twice a day, and 8 mg/d) were also evaluated for PDR prevention; however, with small patient numbers for individual regimens and changing dosage regimens during the study, no statistically significant differences were noted.

VISUAL ACUITY, OCULAR THERAPEUTIC INTERVENTION, AND MACULAR EDEMA

As shown in Table 2, fewer eyes in the rosiglitazone group experienced visual acuity loss of 3 or more lines compared with the control group, regardless of baseline NPDR severity. This difference reached statistical significance overall (Wilcoxon, P = .03; log-rank, P = .03). In eyes without PDR at baseline, fewer eyes in the rosiglitazone group received scatter (panretinal) photocoagulation compared with the control group, but this difference was not statistically significant (rosiglitazone: 9 of 219 [4.1%]; 20 of 259 [7.7%]; P = .09). At baseline, 8 eyes in the rosi-
glitazone group and 28 eyes in the control group had PDR, and no statistical difference was observed regarding need for additional PRP (each 100%), need for vitrectomy, or development of traction retinal detachment.

Rosiglitazone had been reported to be possibly associated with development of DME.24,25 In our study, rosiglitazone was not associated with an increased incidence of CSME in patients without macular edema at baseline (Wilcoxon, $P = .28$; log-rank, $P = .22$) (Figure 2A), nor in patients with milder DME at baseline (Wilcoxon, $P = .29$; log-rank, $P = .58$) (Figure 2B). In the rosiglitazone group, patients with pedal edema were not more likely to develop CSME (10.5% at 3 years’ follow-up) (Figure 2C) than patients without pedal edema (17.9% at 3 years’ follow-up) (Wilcoxon, $P = .54$; log-rank, $P = .10$).

Overall, slightly fewer eyes in the rosiglitazone group received focal/grid laser treatment for macular edema compared with the control group, but this difference was not statistically significant (rosiglitazone: 26 of 196 [13.3%]; 39 of 246 [15.9%]; $P = .45$).

Rosiglitazone is an orally administered PPAR-γ agonist that acts as an insulin sensitizer and is commonly prescribed to control hyperglycemia in patients with diabetes.14-17 Large randomized trials demonstrated that rosiglitazone lowers HbA1c values by 1.2% in patients with a baseline value of 7.5% or greater.26 Rosiglitazone has also been shown to have antiangiogenic properties in laboratory studies.18,21 In this study, we present 3-year follow-up data suggesting that patients with type 2 diabetes who are treated with rosiglitazone may have delayed onset of PDR and less loss of visual acuity. To our knowledge, this is the first study to show evidence of rosiglitazone-mediated antiangiogenesis in humans.

A previous study21 demonstrated that rosiglitazone mediates antiangiogenesis through PPAR-γ activation in endothelial cells, resulting in direct inhibition of endothelial cell proliferation. Rosiglitazone also causes endothelial

**Figure 1.** Effect of rosiglitazone on the onset of proliferative diabetic retinopathy (PDR) by baseline retinopathy severity. Kaplan-Meier survival curves showing cumulative percentage progression to PDR for patients treated with rosiglitazone (RSS) and control patients. The number of eyes in each group with more than 1 follow-up visit (year 0) and at the beginning of each follow-up interval is indicated below the x-axis. A, $P = .045$ by Wilcoxon method, $P = .06$ by log-rank method. B, Wilcoxon, $P = .66$; log-rank, $P = .87$. C, Wilcoxon, $P = .95$; log-rank, $P = .76$. D, Wilcoxon, $P = .12$; log-rank, $P = .17$. NPDR indicates nonproliferative diabetic retinopathy.

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**COMMENT**

Rosiglitazone is an orally administered PPAR-γ agonist that acts as an insulin sensitizer and is commonly prescribed to control hyperglycemia in patients with diabetes.14-17 Large randomized trials demonstrated that rosiglitazone lowers HbA1c values by 1.2% in patients with a baseline value of 7.5% or greater.26 Rosiglitazone has also been shown to have antiangiogenic properties in laboratory studies.18,21 In this study, we present 3-year follow-up data suggesting that patients with type 2 diabetes who are treated with rosiglitazone may have delayed onset of PDR and less loss of visual acuity. To our knowledge, this is the first study to show evidence of rosiglitazone-mediated antiangiogenesis in humans.

A previous study21 demonstrated that rosiglitazone mediates antiangiogenesis through PPAR-γ activation in endothelial cells, resulting in direct inhibition of endothelial cell proliferation. Rosiglitazone also causes endothelial
cell apoptosis via PPAR-γ and maxi-K channels, low-
er vascular endothelial growth factor expression, inhib-
its vascular endothelial growth factor receptors, and in-
creases matrix metalloproteinase inhibitor activity. These various mechanisms are likely of biological im-
portance because the antiangiogenic effect of rosigli-
tzone has been confirmed in animal models and is sug-
gested in this study of humans.

In this study, progression rates to PDR in the control
group were consistent with previous reports. The de-
layed onset of PDR observed with rosiglitazone treat-
ment is unlikely to be a result of altered blood glucose
concentrations because both groups had similar initial
and final HbA1c values. Insulin use was higher in the con-
tral group as expected, since rosiglitazone has been shown
to reduce insulin requirement in patients with type 2 dia-
betes mellitus.

Although well matched for key baseline characteris-
tics relevant to the progression of DR, including dia-
tes type, diabetes duration, HbA1c value, blood pressure,
and visual acuity, the retrospective nature of the study
resulted in some pertinent group differences. On aver-
age, the rosiglitazone group had a higher BMI, better re-
nal function, and less use of antihypertensive medica-
tions. Adverse effects of rosiglitazone, including weight
 gain and pedal edema, may account for the increased BMI
tions. However, without pretreatment BMI data, a direct association cannot be ascertained. The higher
mean BMI in the rosiglitazone group is unlikely to ac-
count for the observed retinopathy benefit because higher
BMI is associated with worsening of retinopathy.

Rosiglitazone use is associated with improved renal func-
tion and antihypertensive effects as observed in our patient groups. Microalbuminuria may be associ-
ated with increased risk of PDR in patients with diabetes. An increased risk of retinopathy progres-
sion is associated with elevated blood pressure but not
with antihypertensive therapy. In our study, both syst-
olic and diastolic blood pressures were well matched be-
tween groups during the follow-up period.

Patients treated with rosiglitazone experienced less loss
of visual acuity than control patients after 5 years, an effect
present regardless of baseline NPDR severity (Wil-
coxon and log-rank tests: \(P = .03\)) (Table 2). Thus, not
all the visual benefit of rosiglitazone may be attributable
to prevention of PDR. Determining the reproducibil-
ity, mechanism, and magnitude of this effect will require larger
prospective studies.

No significant increase in the development of CSME
was observed in the rosiglitazone group despite a few re-
ports suggesting that rosiglitazone may induce or exac-
terate macular edema in patients with diabetes. Pro-
tein kinase C-β activation is postulated as an underly-
ing mechanism. However, a large ongoing prospective clini-
cal trial (Action to Control Cardiovascular Risk in Dia-
betes) evaluated 3468 participants with diabetes (6865
eyes) and did not find an increased risk of CSME associ-
ated with rosiglitazone (oral communication, Emily
Chew, MD, National Eye Institute, May 2006).

Our study has limitations inherent to its retrospec-
tive design and limited patient numbers. Patient num-
bers are limited by the prevalence of rosiglitazone therapy

Figure 2. Effect of rosiglitazone on the development of clinically significant macular edema (CSME). A and B, Kaplan-Meier survival curves showing cumulative percentage progression to CSME in patients treated with rosiglitazone (RSG), who had no macular edema (ME) at baseline (A) or ME but no CSME before treatment (B). C, Patients in the RSG group with pedal edema (PE) and without PE. Number of eyes in each group with more than 1 follow-up visit (year 0) and at the beginning of each follow-up interval is indicated below the x-axis. A, Wilcoxon, \(P = .28\); log-rank, \(P = .22\). B, Wilcoxon, \(P = .27\); log-rank, \(P = .58\). C, Wilcoxon, \(P = .54\); log-rank, \(P = .10\).
in 2003 and the need for medical and ophthalmologic follow-up at the same institution to maximize accurate medical and ocular characterization. Accurate treatment initiation dates of rosiglitazone were not available in some patients who were already receiving therapy before their first visit at Joslin. The relatively small sample size limited study power, particularly with fewer patients completing more than 3 years of follow-up. The usual caveats pertinent to retrospective studies with regard to variability of clinical data recording and collection may also influence the outcome. However, these effects were minimized because of the unique academic setting at the BEI and Joslin: most clinical findings were recorded in standardized electronic medical record templates; visual acuity examiners, refractionists, and visual examination rooms were certified for clinical trials; and BEI staff recorded the severity of retinopathy according to the ETDRS clinical retinopathy grading protocol. Collection of all data was performed using standardized forms. Despite study design limitations, these data provide initial evidence for a possible antiangiogenic effect of rosiglitazone in patients with diabetes. Larger, prospective clinical trials are needed to confirm the role of rosiglitazone in preventing PDR.

Adverse effects of rosiglitazone include peripheral edema (5%-10% of patients), abnormal liver function tests (<1%), and worsening congestive heart failure (<1%). Mild anemia and dose-dependent weight gain of 0.5 to 3.7 kg have been reported. In 1999, rosiglitazone was approved by the US Food and Drug Administration and, in 2001, more than 8 million prescriptions were dispensed. Recently, the safety of rosiglitazone therapy has been questioned in a meta-analysis of 42 of 116 potentially relevant studies, which found that the odds ratio was 1.43 (P = .03) for myocardial infarction and 1.64 (P = .06) for death from cardiovascular causes in patients treated with rosiglitazone. An accompanying editorial identified several study design factors to be considered when assessing these data. A more recent report found that rosiglitazone was not associated with an increase in death from either cardiovascular causes or all causes. However, rosiglitazone was associated with an increased risk of heart failure and the data were insufficient to determine whether there was an associated increase in the risk of myocardial infarction. Additional studies are under way to address the safety issues of this medication in definitive ways.

In light of the recent safety data, careful risk assessment and patient selection will be important for any future studies. However, the potential benefit of rosiglitazone in reducing retinopathy progression and maintaining visual acuity could significantly reduce personal and societal burdens and should be considered if risks can be appropriately managed. In addition, rosiglitazone-mediated antiangiogenesis may have a role beyond the realm of DR, as glitazone treatment has been well tolerated in patients without diabetes in clinical trials. Thus, rosiglitazone may benefit other pathologic angiogenic conditions such as age-related macular degeneration and certain types of cancer.

In conclusion, this study of 282 patients with diabetes with a mean follow-up time of 2.8 years suggests that orally administered rosiglitazone may delay the onset of PDR in patients with severe NPDR at baseline. Rosiglitazone treatment may also be associated with less loss of visual acuity. However, because this study does not rigorously prove that rosiglitazone either reduces the incidence of PDR or prevents loss of visual acuity, and because there may be adverse effects from therapy, rosiglitazone treatment of patients with diabetes specifically to reduce these ophthalmic complications is not advocated at this time. Determination of the full efficacy and clinical role of rosiglitazone in the treatment of PDR and other angiogenic conditions awaits confirmation of risks and benefits and possibly large-scale definitive studies.

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Author Contributions: Drs Shen, Folkman, and Aiello had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported

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Previous Presentation: The results of this study were presented at the annual meeting of the Association for Research in Vision and Ophthalmology; May 2, 2006; Fort Lauderdale, Florida; and received the Dr Henry and Lilian Nesburn Award for the best paper by a resident in June 2007.

Additional Information: This study is dedicated to the memory of David Magoon, who contributed significantly to data collection.

Additional Contributions: Edwin Chen, PhD, provided statistical analysis; Lisa Finston, Garretson Beebe, and Andrew Principe performed data collection; Anne McKay performed electronic data entry; and Om Ganda, MD, provided supporting data.

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