Photodynamic Therapy With Verteporfin for Subfoveal Choroidal Neovascularization in Age-Related Macular Degeneration

Results of an Effectiveness Study

Sanjay Sharma, MD, MSc(Epid), MBA; Jeff Bakal, MSc; Alejandro Oliver-Fernandez, MD, MSc; Jason Blair, BSc, MBA

Objective: To determine the postapproval effectiveness of photodynamic therapy (PDT) with verteporfin for the treatment of predominantly classic subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration.

Methods: Forty-five consecutive patients treated with PDT for subfoveal CNV were compared with an untreated historical control group. Control patients had subfoveal CNV and were first seen by us within 1 year before Health Canada’s approval of verteporfin. Both groups were followed up for the development of significant visual loss, stability, or improvement. Multivariate models were constructed to evaluate the effectiveness of PDT, controlling for multiple covariates (age, sex, baseline visual acuity, follow-up time, lesion size, and number of treatments).

Results: Significant differences were noted in the change in visual acuity between those who did and did not receive PDT ($\chi^2 = 5.9, P = .048$). Patients who received PDT were 2.9 times (95% confidence interval, 0.9-9.1) less likely to develop a moderate (>2 lines) visual loss ($\chi^2 = 3.2, P = .07$). Controlling for covariates, patients who received PDT were 13.7 times (95% confidence interval, 1.4-132.6) more likely to develop a visual improvement of at least 1 line.

Conclusion: Compared with historical controls, PDT was demonstrated to be effective for the treatment of predominantly classic subfoveal CNV.

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Age-related macular degeneration (AMD) is the leading cause of visual loss in people older than 50 years in North America and is associated with significant reductions in quality of life. Because this segment of the population is expected to double in size during the next 25 years, the development of preventive and therapeutic strategies to combat this disease constitutes a pressing concern.

Visual loss from AMD occurs mostly as a result of the development of choroidal neovascularization (CNV). During the 1980s and 1990s, the Macular Photocoagulation Study group established the value of thermal laser photocoagulation for patients with well-circumscribed juxtafoveal and extrafoveal CNV, which constitute 10% to 15% of all neovascular lesions. However, when applied to subfoveal lesions, photocoagulation destroys the photoreceptors overlying the abnormal vessels, leading to immediate and irreversible loss of central vision.

More recently, photodynamic therapy (PDT) was investigated as a therapeutic alternative for these types of lesions because of its potential for reduced photoreceptor damage. Data from the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) investigation demonstrated a reduction of visual loss in patients with predominantly classic subfoveal CNV who received verteporfin PDT, compared with controls. As a result, PDT has been approved in more than 40 countries, including Canada and the United States, for treatment of predominantly classic subfoveal CNV secondary to AMD.

Randomized clinical trials represent the highest quality of evidence available to evaluate treatment benefit. By definition, these studies use randomization to assign patients to treatment or control groups, thereby minimizing the selection bias that plagues most other study designs. Randomized clinical trials also control for a host of covariates by using stringent patient selection criteria and a rigid treatment protocol. With this powerful experimental design, randomized clinical trials are ideally suited to determine a treatment’s efficacy, ie, the way in which it...

From the Departments of Epidemiology and Ophthalmology (Dr Sharma) and Mathematics and Statistics (Mr Bakal), Queen’s University, and the Cost-Effective Ocular Health Policy Unit, Hotel Dieu Hospital (Drs Sharma and Oliver-Fernandez and Messrs Bakal and Blair), Kingston, Ontario. The authors have no relevant financial interest in this article.
works under ideal circumstances when delivered to select patients by providers most skilled at providing it. Such rarified conditions, however, can severely limit the generalizability of a study’s results to the general population in a more natural situation. In “real-life” settings, the patients being treated tend to have more advanced disease and be less compliant. Furthermore, the resources available to implement a given treatment may be partially or totally unavailable.

A treatment’s performance under ordinary conditions by the average practitioner and delivery system can be referred to as its effectiveness. Observational studies that follow up patients over time to measure the strength of the association between treatment and effect can be used to evaluate a treatment’s effectiveness. Such studies, which can be prospective or retrospective in nature, usually lack randomization of treatment and therefore cannot definitively establish a cause-and-effect relationship. Nevertheless, they typically use a control group of patients that allows consideration of several important confounding variables by means of established statistical methods. Therefore, effectiveness studies complement the information obtained from a randomized clinical trial by informing about a treatment’s outcomes in clinical practice.

Although there is little doubt that the results of the TAP investigation demonstrated the safety and efficacy of PDT via its 2 concurrently run randomized clinical trials, 2 questions remain to be answered before PDT can be fully advocated. First, it must be established whether the observed benefits in vision translate into significant gains in quality of life for patients. As previously shown through the use of Markov modeling and simulation, that is likely to be the case. Second, it must be established whether an intervention’s efficacy can be generalized to other health care settings and patient populations. One way of doing so is through the use of observational studies like the present one, which can analyze a treatment’s effectiveness in a real-life situation. The objective of this study was to evaluate the effectiveness of PDT with verteporfin in a tertiary care practice for the treatment of predominantly classic CNV secondary to AMD.

**METHODS**

This study, which was approved by the Queen’s University Research Ethics Board, was conducted following Health Canada’s approval for use of verteporfin in PDT for the treatment of predominantly classic subfoveal CNV secondary to AMD.

Our treatment group consisted of 45 consecutive patients who underwent PDT for predominantly classic subfoveal CNV by one of us (S.S.) at a tertiary care retinal practice, between November 12, 2000, and November 21, 2001. Patients with non–age-related causes of CNV (eg, myopia, angioid streaks, ocular histoplasmosis, and trauma), as well as those with greater than 50% occult CNV, were excluded from this study.

Photodynamic therapy was administered as per the TAP investigation protocol. Specifically, verteporfin was administered in a 10-minute infusion delivered through the antecubital vein, followed by 83 seconds of 689-nm laser treatment. Adverse reactions observed during the procedure were documented. Patients were followed up for at least 3 months at 3-month intervals, at which time they had Snellen visual acuity testing, a stereoscopic fundus examination, and digital angiography performed. Patients with persistent intraretinal or subretinal fluid (as identified by a stereoscopic contact examination with a contact lens) and persistent angiographic leakage of the lesion were offered additional treatment with PDT. Reasons for not offering additional treatment included complete angiographic closure of the CNV, complete elimination of intraretinal or subretinal macular fluid, or subjective worsening of vision greater than 3 lines following treatment.

The primary clinical outcomes analyzed were (1) overall change in visual acuity, (2) likelihood of developing moderate (>2 lines) visual loss, and (3) likelihood of gaining at least 1 line of visual acuity, as measured by Snellen visual acuity testing.

We compared the visual progress of our patients with a group of historical control subjects, who were selected in a consecutive fashion from a database of an ongoing study evaluating the quality of life related to AMD. The patients selected from this database had subfoveal CNV and were first seen by us before the approval of PDT with verteporfin by Health Canada. All of these patients had no treatment performed for their lesions. Patients in this group manifested lesions between June 1, 1999, and June 1, 2000, and were followed up for at least 4 months.

An observer (A.O.-F.) who was not involved in patient treatment collected data from standardized forms that were filled out at the time of assessment in the treatment group and at a point following the visit in the control group. The following information was abstracted from patients’ medical charts: age, sex, baseline visual acuity, duration of follow-up, size of the lesions, number of treatments, and visual acuities at the different follow-up times. All data were entered into Excel 2000 (Microsoft Corp, Redmond, Wash) and SPSS 10.0 for Windows (SPSS Inc, Chicago, Ill) spreadsheets.

Baseline data were analyzed by means of t tests for continuous variables and χ² tests for dichotomous variables. Uncontrolled differences in visual acuity change and improvement in visual acuity between groups were evaluated using odds ratios and goodness-of-fit analysis. The effect of PDT on changes in visual acuity, controlling for all known potential covariates (age, sex, baseline visual acuity, duration of follow-up, size of the lesions, and number of treatments), was evaluated by analysis of variance (ANOVA) testing. Logistic regression analysis was performed to estimate the likelihood of a gain in visual acuity across the range of clinical variables. All analyses were performed by one of us (Mr Bakal) who was not involved in patient care, data abstraction, or data recording and who was masked to treatment allocation. (Allocation data were recorded by the data abstractor [A.O.-F.] as 0 for PDT and 1 for natural history.)

**RESULTS**

Forty-nine consecutive patients who received PDT were recruited into the study, 4 of whom were lost to follow-up after the initial treatment. A search of our quality-of-life database yielded 49 control patients. However, a review of their angiograms revealed that only 34 (69%) had the predominantly classic form of subfoveal CNV. Patients in the treatment group received a mean of 3.3 treatments during a mean period of 13 months. As seen in Table 1, the treatment and control groups were comparable in terms of age, sex, follow-up time, lesion size, and baseline visual acuity.

A comparison of the net change in visual acuity of the treatment and control groups showed them to differ
allocated (PDT vs observation) explained a significant proportion of this ANOVA demonstrated that the type of treatment acuity that were measured during the study. The results of this ANOVA showed that the mean change in visual acuity was -0.21 with a 95% confidence interval of -0.29 to -0.14 (F=34.02, P<.001).

To further test the association between vision improvement and treatment, controlling for the effects of other variables, we next performed a logistic regression analysis. This test showed that patients who received PDT with verteporfin were 13.7 times (95% confidence interval, 1.4-132.6; P=0.02) more likely to develop a visual improvement of 1 or more lines of vision (Table 3). In fact, of all the independent variables tested, treatment allocation was the best predictor of visual improvement (β=2.62). None of the other variables analyzed achieved statistical significance in our model.

In the 138 administered treatments, 11 complications were documented. The most frequent complication was infusion-related back pain, which occurred in 7 instances (5%). Also documented were lightheadedness (1 [0.7%]), joint pain (1 [0.7%]), hearing loss (1 [0.7%]), and transient double vision (1 [0.7%]).

Like the TAP investigation, our study assessed the proportion of patients with predominantly classic CNV secondary to AMD who developed changes in their visual acuity following PDT or no treatment. Unlike the TAP investigation, our treatment allocation was not random in nature, as our study was conducted following Health Canada’s approval of PDT. Despite this and other implicit differences in study design, our study also demonstrated a 2-fold reduction in risk (relative risk, 2.2; P=.048; log linear analysis = 5.58, P=.008) (Table 2). Although 13 (38%) of 34 control patients progressed to a loss of 3 or more lines of vision, this occurred in only 8 (18%) of 45 treated patients. This constitutes a 2-fold reduction in risk (relative risk, 2.2; 95% confidence interval, 0.9-5.1) for moderate visual loss in treated patients (χ²=3.2, P=.07). Conversely, none of the control patients exhibited visual acuity gains beyond 2 lines, while 3 (7%) of those receiving PDT did. Furthermore, a statistically significant difference in the proportion of patients who gained 1 or more lines of vision in each group was noted (3% [1/34] vs 22% [10/45]; χ²=6.1, P=.02; Fisher exact test) (Table 3).

To determine the simultaneous effect of patient characteristics and treatment on visual acuity, we performed 2 types of multivariate analysis. First, we used ANOVA to isolate and assess the relative contribution of patient age, sex, baseline visual acuity, lesion size, length of follow-up, and number of treatments to the changes in visual acuity that were measured during the study. The results of this ANOVA demonstrated that the type of treatment allocated (PDT vs observation) explained a significant proportion of the variation in visual acuity (F=7.13, P=.008) (Table 4). This effect was second only to that attributable to the baseline visual acuity (F=34.02, P<.001), and no other measured attributes suggested any effect on visual improvement.

To further test the association between vision improvement and treatment, controlling for the effects of other variables, we next performed a logistic regression analysis. This test showed that patients who received PDT with verteporfin were 13.7 times (95% confidence interval, 1.4-132.6; P=0.02) more likely to develop a visual improvement of 1 or more lines of vision (Table 5). In fact, of all the independent variables tested, treatment allocation was the best predictor of visual improvement (β=2.62). None of the other variables analyzed achieved statistical significance in our model.

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Table 1. Baseline Characteristics of the Treatment and Control Groups*  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>Control</th>
<th></th>
<th>P Value (SE)</th>
<th>Value (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>77 (8.1)</td>
<td>79 (59)</td>
<td>20-89</td>
<td>.28</td>
<td></td>
</tr>
<tr>
<td>Male/female, No.</td>
<td>15/30</td>
<td>15/19</td>
<td></td>
<td>.31†</td>
<td></td>
</tr>
<tr>
<td>Baseline visual acuity, logMAR</td>
<td>-2.3 (1.16)</td>
<td>-2.61 (1.75)</td>
<td>0 to -3</td>
<td>.34</td>
<td></td>
</tr>
<tr>
<td>Follow-up time, mo</td>
<td>13.0 (5.5)</td>
<td>13.5 (10.0)</td>
<td>4-48</td>
<td>.82</td>
<td></td>
</tr>
<tr>
<td>Greatest linear dimension of lesion, mm</td>
<td>3.70 (1.65)</td>
<td>3.67 (1.40)</td>
<td>1.0-7.2</td>
<td>.92</td>
<td></td>
</tr>
</tbody>
</table>

*Data are given as mean (SD) [range] unless otherwise indicated.

Table 2. Difference in Visual Acuity Change Between the Treatment and Control Groups*  

<table>
<thead>
<tr>
<th>Group</th>
<th>≥3 Lines Lost</th>
<th>2 Lines Lost</th>
<th>≥3 Lines Gained</th>
<th>3 Lines Gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n = 45)</td>
<td>8 (18)</td>
<td>34 (70)</td>
<td>3 (7)</td>
<td></td>
</tr>
<tr>
<td>Control (n = 34)</td>
<td>13 (38)</td>
<td>21 (62)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Data are given as number (percentage).

Table 3. Difference in Visual Acuity Gain of ≥1 Lines Between the Treatment and Control Groups*  

<table>
<thead>
<tr>
<th>Group</th>
<th>Improvement</th>
<th>No improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n = 45)</td>
<td>10 (22)</td>
<td>35 (78)</td>
</tr>
<tr>
<td>Control (n = 34)</td>
<td>1 (3)</td>
<td>33 (97)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage).

Table 4. Analysis of Variance in Visual Acuity (VA) Change Between the Treatment and Control Groups  

<table>
<thead>
<tr>
<th>Variable</th>
<th>SS</th>
<th>df</th>
<th>MS†</th>
<th>F Value†</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline VA</td>
<td>11.60</td>
<td>1</td>
<td>11.60</td>
<td>34.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Treatment</td>
<td>2.45</td>
<td>1</td>
<td>2.45</td>
<td>7.13</td>
<td>.008</td>
</tr>
<tr>
<td>Age</td>
<td>0.14</td>
<td>1</td>
<td>0.14</td>
<td>0.41</td>
<td>.52</td>
</tr>
<tr>
<td>Sex</td>
<td>0.30</td>
<td>1</td>
<td>0.45</td>
<td>1.30</td>
<td>.26</td>
</tr>
<tr>
<td>Greatest linear dimension of lesion, mm</td>
<td>0.21</td>
<td>1</td>
<td>0.21</td>
<td>0.62</td>
<td>.43</td>
</tr>
<tr>
<td>Error</td>
<td>24.60</td>
<td>71</td>
<td>0.343</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>188.90</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrected total</td>
<td>43.49</td>
<td>76</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MS, mean square; SS, sum of squares.
+R² = 0.44.
†Ellipses indicate data not available.
strated differences in vision between the treatment and historical control groups ($\chi^2 = 5.85$, $P = .048$).

Following a mean of 3.3 treatments and 13 months of follow-up, patients undergoing PDT with verteporfin were 2.9 times (95% confidence interval, 0.9-9.1) less likely to develop moderate visual loss ($\chi^2 = 3.2$, $P = .07$). These results are comparable to those obtained in the TAP investigation, with a mean of 2.7 treatments. In fact, using a multivariate analysis to control for potential confounders in our study, those who received PDT were 14.5 times more likely to improve their vision ($P = .02$). This was corroborated by ANOVA, which showed that treatment differences explained a large proportion of the change in visual acuity ($F = 7.13$, $P = .008$) in our study population. In addition, similar to the TAP investigation, we found a low incidence of local and systemic adverse effects in those who received verteporfin therapy.

Our study has potential limitations. First, as with the TAP study, we are unable to predict the long-term effectiveness of this treatment; only ongoing evaluation of these cohorts will allow for the evaluation of the long-term stability of our results. In addition, our analyses did not control for diet or the use of vitamin supplementation, both of which may have affected the relationship that exists between treatment allocation and primary outcome.

In conclusion, these findings suggest that the beneficial visual outcomes reported by the TAP investigators can be reproduced in a tertiary ophthalmic practice. In addition, visual improvement was significantly more likely to occur in those patients with predominantly classic subfoveal CNV.

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Corresponding author and reprints: Sanjay Sharma, MD, MSc(Epid), Cost-Effective Ocular Health Policy Unit, Hotel Dieu Hospital, Brock II-224B, 166 Brock St, Kingston, Ontario, Canada K7L 5G2 (e-mail: sanjay_sharma60@hotmail.com).

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