A Model of the Incidence and Consequences of Choroidal Neovascularization Secondary to Age-related Macular Degeneration

Comparative Effects of Current Treatment and Potential Prophylaxis on Visual Outcomes in High-Risk Patients

Diana M. Lanchoney, MD; Maureen G. Maguire, PhD; Stuart L. Fine, MD

**Objective:** To describe the comparative impact of current and preventive treatments on incidence of choroidal neovascularization (CNV) and severe vision loss in patients with bilateral soft drusen (BSD).

**Design:** Stochastic model.

**Setting:** US population.

**Patients:** Prevalence cohort of white patients 43 years or older with BSD.

**Interventions:** Application of prophylaxis of 10% to 50% efficacy to 1 or both eyes of patients with BSD, application of laser photocoagulation to eligible CNV lesions, or both.

**Main Outcome Measures:** Proportion of patients with BSD after 10 years with unilateral and bilateral CNV and resultant unilateral and bilateral vision loss to visual acuity of 20/200 or worse.

**Results:** The natural history of patients with BSD generated by the model shows that 12.40% of these patients develop either unilateral or bilateral CNV within 10 years of their entry into the BSD prevalence cohort. Bilateral disease occurs in 3.86% of patients with BSD within 10 years. The proportion of patients with BSD becoming legally blind from CNV within 10 years is 2.54% if no treatment is performed. Current laser treatment for CNV decreases the proportion with legal blindness within 10 years to 2.24%. The addition of a preventive treatment of 10% efficacy applied bilaterally to the current laser treatment regimen decreases the proportion with legal blindness to 1.86%; a 25% effective preventive treatment decreases it to 1.34%. Comparatively, preventive treatment of 10% and 25% efficacy given to the fellow eye only after the first eye has developed CNV decreases the proportion of legally blind patients at 10 years only to 2.06% and 1.77%, respectively. All outcomes vary with sex and age at entry into the BSD cohort.

**Conclusions:** Patients with BSD face a 12.40% risk of developing CNV within 10 years. The addition of even a modest (10% effective) bilateral preventive treatment to the current regimen for CNV would more than double the prevention of legal blindness in the BSD population relative to current laser treatment; a preventive treatment of 33% efficacy more than halves the rate of legal blindness caused by CNV. Preventive treatment given to the fellow eye only after the first develops CNV has substantially less impact.


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**Clinical Sciences**

From the Scheie Eye Institute, Department of Ophthalmology, University of Pennsylvania Health System, Philadelphia.

A**GE-RELATED** macular degeneration is the leading cause of visual loss in people older than 65 years in the United States.\(^1\) While geographic atrophy can cause severe vision loss, approximately 90% of the severe vision loss associated with age-related macular degeneration results from choroidal neovascularization (CNV).\(^2\) The current treatment regimen of laser photocoagulation for CNV is applicable only to a small percentage of afflicted patients\(^3-5\) and is only modestly effective.\(^6-12\) There has, therefore, been interest in the development of preventive treatments, such as nutritional supplements\(^13,14\) and light laser photocoagulation,\(^15,16\) for patients at high risk.

Eyes with large, soft drusen develop CNV at higher than average rates, especially if the fellow eye already has CNV.\(^17,18\) Patients with bilateral soft drusen (BSD) may be good candidates for effective preventive treatments. However, there is little information about the prognosis of patients with BSD. Previous investigators have observed rates of CNV development in high-risk eyes for only 3 to 5 years; their longer-term prognosis is therefore unclear.\(^2,19,20\) These studies also focused on the outcomes of eyes (eg, the incidence of CNV) rather than patients (eg, the incidence of CNV-induced legal blindness). This lack of information raises important questions about how to counsel patients with BSD about their prognosis for vi-
PATIENTS AND METHODS

The model, written on Excel software (Microsoft Corp, Seattle, Wash), is designed to assess the morphologic and functional outcomes of eyes in a cohort of patients with BSD. This BSD prevalence cohort faces risks of death, development of CNV, and development of severe vision loss (best-corrected visual acuity of 20/200 or worse) each year (Figure 1). At the end of the year, each patient is classified as alive or dead. Each eye is classified on a morphologic basis as having CNV or not and on a functional basis as having severe vision loss or not. Laser treatment of patients developing CNV is incorporated into the model by allowing the risk of developing severe vision loss to depend on treatment status. Preventive treatments are incorporated into the model by allowing the risk of developing CNV in one or both eyes to depend on preventive treatment status and the treatment’s assumed effectiveness. The major assumptions of the model are noted in Table 1 and Table 2. As the model represents a computerized manipulation of published data, no informed consent from any patient was indicated or obtained.

POPULATION WITH BSD

The population at risk is designed to be representative of the current US population with BSD at risk for CNV. The population is formed by applying the age- and sex-specific prevalence rates of BSD observed in Beaver Dam, Wis, to the white US population older than 45 years (Ronald Klein, MD, oral communication, April 1, 1996).

MORTALITY

United States age- and sex-specific mortality rates (for ages at 10-year intervals) for whites are applied. Mortality is assumed to be unaffected by morphologic and functional state.

CHANGE IN MORPHOLOGIC STATE: DEVELOPMENT OF CNV

The risk of CNV’s developing in an eye of a patient with BSD is based on the rates observed in follow-up studies of patients with BSD. Within the BSD population, the incidence of CNV does not vary with age or sex. The rate of CNV development in the first eye is reduced after 5 years to 75% of the initial rate demonstrated in follow-up studies and to 50% of the initial rate after 10 years. After 1 eye of a patient develops CNV, the risk of developing CNV in the second eye is based on rates observed in follow-up studies of patients with unilateral CNV. Conversion of all observed cumulative incidence rates to annualized incidence rates is based on the model \[ CI = 1 - \exp(-R(t)) \], where CI represents cumulative incidence; R, annual incidence; and t, the time in years during which the cumulative incidence rate was measured.

When preventive treatment effects on the rate of CNV development are considered, they are modeled as a reduction in the base rates (as determined above) by a percentage equal to the assumed efficacy of the preventive treatment.

CHANGE IN FUNCTIONAL STATE: DEVELOPMENT OF SEVERE VISION LOSS

The risk of developing severe vision loss in eyes with CNV is based on follow-up studies of CNV lesions. The annual risk of severe vision loss in eyes with CNV depends on the lesion type (occult, classic, or mixed) and location (juxtapapillary, juxtafoveal, or subfoveal). A single, composite rate is formed using a weighted average of the annualized incidence rates of severe vision loss in eyes with the varieties of CNV as listed above; the weights reflect the relative frequency of the lesion types and locations. The model reflects a decrease in risk of severe vision loss after 3 years, in accordance with published data.

The current impact of laser treatment on vision is estimated from the effect of treatment on particular types of CNV lesion. Published estimates of the proportion of lesions that are eligible for laser treatment vary from 13% to 41% of active CNV lesions. The model uses the highest published proportion (41%) of treatment eligibility for 2 reasons. First, the calculated benefits of preventive treatment relative to the benefits of current laser treatment are conservatively estimated when a higher number of lesions are considered treatable. Second, the case series that presented the lowest proportion of treatable lesions (13%) did not include any untreatable subfoveal classic lesions. Because untreated subfoveal classic lesions have the worst visual prognosis of all CNV lesions, eliminating them from our composite risk of vision loss seemed unrealistic. Thus, studies by Moisseiev et al and Bressler et al were used for an indication of both clinical frequency of lesion types and treatment eligibility. For internal consistency, we chose to use only 1 set of these data (Moisseiev); this source provided data similar to that offered by Bressler.

The impact of treatment on rates of severe vision loss is based on follow-up studies of treated lesions of various types (Table 2). For purposes of generating a natural history model, a composite rate of vision loss is generated; the rate is based on an average of all treated and untreated lesions weighted by the frequency of the corresponding lesion type and location. In accordance with published data, risks of vision loss for the first 3 years after CNV development and for years 4 and beyond are again calculated separately.

SENSITIVITY ANALYSIS

A sensitivity analysis is performed by altering several key factors in the model over the range of 50% to 150% of their assumed values (Table 2). These variables are listed below, each followed by their assumed values used in this article as well as the range considered in the sensitivity analysis: the annual rate of CNV development in the first eye (assumed value, 1.00%; range, 0.30%-1.30%), the annual rate of CNV development in the second eye for years 1 through 3 (assumed value, 1.00%; range, 5.10%-15.23%) and year 4 and after (assumed value, 6.56%; range, 3.28%-9.84%), the risk of severe vision loss from treatable CNV for years 1 through 3 (assumed value, 27.66%; range, 13.83%-41.49%) and year 4 and after (assumed value, 6.39%; range, 3.18%-9.53%), the risk of severe vision loss from
untreatable CNV for years 1 through 3 (assumed value, 48.11%; range, 24.05%-72.17%) and year 4 and after (assumed value, 9.30%; range, 4.75%-14.29%), and the proportionate rate of CNV development in the first eye at year 6 compared with the rate used for years 1 through 5 (assumed value, 75.00%; range, 37.50%-112.50%). We examine how changes in these variables over the stated ranges alter the average proportion of patients with BSD developing legal blindness within 10 years, assuming current treatment is applied; this value (discussed in the “Results” section) is 2.24% when all variables are given their assumed values (referred to as the base case). We define as sensitive those variables that produce a change of greater than 10% (range, 2.02%-2.46%) in the value of this outcome as generated in the base case.

Quantifying the potential benefits of prophylaxis in terms of prevention of severe, bilateral, vision loss would clarify how delivery of effective preventive treatment would translate into blindness prevention in a high-risk group such as the BSD population. Since drusen do not cause severe vision loss and the elderly population developing CNV faces high annual mortality rates, the relative value of treating patients with BSD as opposed to the smaller group developing unilateral CNV remains undefined.

To explore these issues, we present a model to describe the natural history of patients with BSD and the comparative effects of current treatment and prophylaxis on their visual outcomes.

**RESULTS**

**NATURAL HISTORY: MORPHOLOGIC INVOLVEMENT**

Figure 2 represents the natural morphologic history of patients with BSD in the United States. Within 10 years, the proportion of the BSD cohort developing CNV in either or both eyes is 12.40%. However, the risk varied from 8.62% to 15.87%, depending on patient sex (Table 3) and age (Figure 3) at entry into the BSD cohort because of different mortality rates. The lowest rate of mortality (that for women aged 43-54 years) induces the highest proportion that develop the disease, because the patients are exposed to the risk of disease development longer before death occurs. Within 25 years of entry into the BSD cohort, an average 16.55% of patients will develop CNV in 1 or both eyes. Again, the range of the proportion affected varied with the age and sex of the patients modeled from 9.41% to 26.32%. For each age category, women have a slightly higher risk of disease than men because of their lower mortality rate.

The development of bilateral CNV is described in Table 3. The model predicts that 3.05%-15.89% of patients with BSD will have developed unilateral CNV for years 1 through 3 (assumed value, 75.00%; range, 37.50%-112.50%). We examine how changes in these variables over the stated ranges alter the average proportion of patients with BSD developing legal blindness within 10 years, assuming current treatment is applied; this value (discussed in the “Results” section) is 2.24% when all variables are given their assumed values (referred to as the base case). We define as sensitive those variables that produce a change of greater than 10% (range, 2.02%-2.46%) in the value of this outcome as generated in the base case.

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The development of bilateral CNV is described in Table 3. The model predicts that 3.05%-15.89% of patients with BSD will develop bilateral CNV within 10 years, ranging from 2.26% to 5.39% depending on sex and age at entry into the cohort. Thus, by the 10-year mark, roughly 30% of the patients who have developed any CNV will have developed bilateral disease, while the other 70% will have developed unilateral disease only. Within 25 years, 8.01% (range, 3.05%-15.89%) of patients with BSD will have developed bilateral CNV, nearly half of those developing any CNV.
Table 2. Quantitative Assumptions

<table>
<thead>
<tr>
<th>Population at risk</th>
<th>Age and sex distribution of model bilateral soft drusen (BSD) population22,*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Entry Into BSD</td>
<td>Population, %</td>
</tr>
<tr>
<td>Prevalence Cohort, y</td>
<td>Women</td>
</tr>
<tr>
<td>43-54</td>
<td>3.2</td>
</tr>
<tr>
<td>55-64</td>
<td>8.7</td>
</tr>
<tr>
<td>65-74</td>
<td>17.5</td>
</tr>
<tr>
<td>≥75</td>
<td>34.7</td>
</tr>
</tbody>
</table>

A total of 100% of BSD population promptly seeks and receives prophylaxis.

Development of choroidal neovascularization (CNV)
Detection of CNV by an ophthalmologist is 100% sensitive and specific
Risk of development of CNV, per eye, per year
First eye (no CNV present)23 = 1.0%
Fellow eye (contralateral CNV)14 = 10.2% from year 1-3 after first eye develops CNV
= 6.6% thereafter

A 10% effective prophylaxis represents the reduction of the rate of development of CNV in an eye to 90% of its value without prophylaxis; similar calculations apply for other prophylactic efficacies

Development of severe vision loss
Risk of severe vision loss (best corrected visual acuity of 20/200 or worse) resulting from drusen only, per year = 0.0%17
Annual risk of severe vision loss resulting from CNV, per year, as per natural history3,6-12,23

<table>
<thead>
<tr>
<th>Lesion Location, Type</th>
<th>Initial Frequency Among All CNV Lesions, %</th>
<th>Annual Rate of Severe Vision Loss Years 1-3 After Development</th>
<th>Frequency Among CNV Lesions Not Already Causing Severe Vision Loss at Year 4 After Development, %</th>
<th>Annual Rate of Severe Vision Loss Year 4 and Later After Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrafoveal, classic</td>
<td>12.7</td>
<td>0.214</td>
<td>23.3</td>
<td>0.094</td>
</tr>
<tr>
<td>Juxtafoveal, classic</td>
<td>11.1</td>
<td>0.277</td>
<td>15.9</td>
<td>0.096</td>
</tr>
<tr>
<td>Subfoveal, classic</td>
<td>34.9</td>
<td>0.728</td>
<td>2.7</td>
<td>0.189</td>
</tr>
<tr>
<td>Occult</td>
<td>30.2</td>
<td>0.309</td>
<td>37.6</td>
<td>0.095†</td>
</tr>
<tr>
<td>Mixed (classic and occult)</td>
<td>11.1</td>
<td>0.212</td>
<td>20.6</td>
<td>0.095†</td>
</tr>
<tr>
<td>Weighted average</td>
<td>100.0</td>
<td>0.429</td>
<td>100.0</td>
<td>0.097</td>
</tr>
</tbody>
</table>

Annual risk of severe vision loss from CNV assuming current laser treatment is given when possible.

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Initial Frequency Among All CNV Lesions, %</th>
<th>Annual Rate of Severe Vision Loss Years 1-3 After Development, %</th>
<th>Frequency Among CNV Lesions Not Already Causing Severe Vision Loss at Year 4 After Development, %</th>
<th>Annual Rate of Severe Vision Loss Year 4 and Later After Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated CNV3,6-12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrafoveal, classic</td>
<td>30.8</td>
<td>0.116</td>
<td>50.1</td>
<td>0.074</td>
</tr>
<tr>
<td>Juxtafoveal, classic</td>
<td>26.9</td>
<td>0.200</td>
<td>32.5</td>
<td>0.082</td>
</tr>
<tr>
<td>Subfoveal, classic‡</td>
<td>42.3</td>
<td>0.442</td>
<td>17.4</td>
<td>0.000</td>
</tr>
<tr>
<td>Weighted average</td>
<td>100.0</td>
<td>0.277</td>
<td>100.0</td>
<td>0.064</td>
</tr>
<tr>
<td>Untreated CNV3,12,23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subfoveal, classic</td>
<td>29.7</td>
<td>0.950</td>
<td>0.01</td>
<td>0.000</td>
</tr>
<tr>
<td>Occult only</td>
<td>51.4</td>
<td>0.309</td>
<td>64.6</td>
<td>0.095†</td>
</tr>
<tr>
<td>Mixed (classic and occult)</td>
<td>18.9</td>
<td>0.212</td>
<td>35.4</td>
<td>0.095†</td>
</tr>
<tr>
<td>Weighted average</td>
<td>100.0</td>
<td>0.481</td>
<td>100.0</td>
<td>0.095</td>
</tr>
</tbody>
</table>

*From Ronald Klein, MD (oral communication, April 1996).
†Exact data unavailable; this figure represents an average of rates from year 4 and later from extrafoveal and juxtafoveal classic lesions.
‡Any lesion with less than 2 Macular Photocoagulation Study (MPS) disc areas or more than 2 MPS disc areas with visual acuity of 20/200 or worse was considered treatable; all other subfoveal classic lesions were considered untreatable.

NATURAL HISTORY: SEVERE VISION LOSS

Legal blindness affects 2.54% of all patients with BSD within 10 years; the range by age and sex characteristics is 1.43% to 3.62% as shown in Table 3. That proportion increases to 6.31% (range, 2.12%-13.29%) when projected for 25 years. Again, groups with the highest mortality (such as men 75 years and older at entry into the BSD cohort) show little increase between 10 and 25 years because most members die within the additional 15-year period if not during the first 10 years. Table 3 details development of legal blindness in 8 age- and sex-specific groups.

Unilateral severe vision loss affects even more patients. Within 10 years, an additional 7.73% of patients with BSD (range, 5.37%-9.88%) can expect to lose vision to a level of 20/200 or worse in 1 eye. Thus, at the 10-year mark, 10.28% of patients with BSD (range, 6.80%-...
13.50%) have experienced some severe vision loss, either unilateral or bilateral. This proportion increases to 14.79% (range, 7.69%-24.73%) after 25 years of natural history. The wide range illustrates the notable impact of age at entry into the cohort on long-term visual prognosis.

CURRENT TREATMENT: EFFECTS ON VISUAL OUTCOMES

Current laser treatment reduces the proportion of patients with BSD who become legally blind within 10 years from 2.54% (range, 1.43%-3.62%) to 2.24% (range, 1.26%-3.20%) as shown in Table 4. Within 25 years, the proportion of patients legally blind decreases from 6.31% (range, 2.12%-13.29%) to 5.71% (range, 1.89%-12.16%) with laser treatment. The modest impact reflects the fact that benefits are conferred to, at most, 41% of all CNV lesions (the highest observed rate of lesion eligibility for treatment per Macular Photocoagulation Study Group guidelines)\(^3\) and that treatment effectiveness in the prevention of legal blindness alone, rather than other gradations of severe vision loss, is considered.

PREVENTIVE TREATMENT: EFFECTS ON MORPHOLOGIC INVOLVEMENT

Table 4 describes the impact of various prophylactic regimens and treatment efficacies on the cumulative proportion of patients with BSD who develop either unilateral or bilateral CNV. When preventive treatment is given to both eyes, the 10-year proportion of patients developing either unilateral or bilateral disease decreases from 12.40% (with laser treatment alone) to 11.24% with a prophylactic treatment of only 10% efficacy, 9.47% with prophylaxis of 25% efficacy, 8.51% with prophylaxis of 33% efficacy, and 6.43% with prophylaxis of 50% efficacy. Comparatively, when the same prophylaxis is given only to the second eye at the time of development of CNV in the first eye, no change is observed in the proportion of patients developing any CNV because the preventive treatment only protects the second eye.

The results change when considering the outcome of bilateral CNV, as described in Table 4. When prophylaxis is given to both eyes at the time of entry into the cohort, the proportion of patients developing bilateral CNV decreases from 3.86% with current treatment to

**Table 4. Percentage of Patients With BSD Who, If Untreated, Live to Develop CNV or Visual Acuity of 20/200 or Worse\(^*\)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age at Entry Into BSD Cohort, y</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNV in 1 or 2 eyes at 10 y</td>
<td>43-54</td>
<td>15.9</td>
<td>15.7</td>
</tr>
<tr>
<td>CNV in 2 eyes at 10 y</td>
<td>55-64</td>
<td>15.5</td>
<td>15.0</td>
</tr>
<tr>
<td>CNV in 2 eyes at 25 y</td>
<td>65-74</td>
<td>14.6</td>
<td>13.6</td>
</tr>
<tr>
<td>Legal blindness at 10 y</td>
<td>&gt;75 y</td>
<td>10.1</td>
<td>8.6</td>
</tr>
<tr>
<td>Legal blindness at 25 y</td>
<td>48.6</td>
<td>12.4</td>
<td></td>
</tr>
</tbody>
</table>

*BSD indicates bilateral soft drusen; CNV, choroidal neovascularization.
3.21%, 2.32%, 1.89%, or 1.10% for 10%, 25%, 33%, and 50% effective preventive treatments, respectively. In comparison, prophylaxis given only to the second eye reduces the proportion of patients developing bilateral CNV only to 3.55%, 3.06%, 2.78%, or 2.16% for 10%, 25%, 33%, and 50% effective prophylaxis, respectively.

PREVENTIVE TREATMENT:
EFFECTS ON VISUAL PROGNOSIS

Table 4 outlines the impact of various prophylactic regimens on the outcome of legal blindness in patients with BSD. Current laser treatment alone yields a 11.81% decrease in the proportion of patients with BSD developing legal blindness caused by CNV within 10 years of cohort entry from 2.54% to 2.24%. A 10% effective prophylaxis given to both eyes in addition to the current laser regimen produces an incremental 16.96% drop from the laser-only rate from 2.24% to 1.86%. Within 10 years of its implementation, a 10% effective treatment would more than double the prevention of legal blindness in the US BSD population achieved by the current treatment regimen. Within 25 years, preventive treatment would reduce the rate of legal blindness from 5.71% to 4.86%, a nearly 15% reduction.

Comparatively, the addition of a 10% effective prophylaxis given only to the second eye after the first develops CNV produces an incremental 16.96% drop from the laser-only rate to 2.24% from 2.86%. Within 10 years of its implementation, a 10% effective treatment would more than double the prevention of legal blindness in the US BSD population achieved by the current treatment regimen. Within 25 years, preventive treatment would reduce the rate of legal blindness from 5.71% to 4.86%, a nearly 15% reduction.

VALIDATION

The model’s validity depends on the accuracy of the rates chosen for disease progression. The rates chosen (from published data) for use in the model produce both incidence and prevalence rates of CNV consistent with independently published observations. The model predicts the 5-year incidence of CNV within the BSD population as 8.10%. This figure is consistent with the 7.1% observed rate in patients with bilateral drusen in the Beaver Dam study by Klein et al.28

Prevalence of CNV within the BSD population was estimated by summing the annual prevalences of CNV from 50 cohorts in which the effects of mortality were accommodated. We chose to examine 50 years’ worth of prevalence because, for a cohort of patients with BSD aged 45 and older, 50 years is a sufficient length of time to allow for the death of almost all of its members. These calculations predict that, at any given time, 18.05% of the live BSD population would have CNV. Because the BSD population forms 6.69% of the general population,28 this corresponds to 1.21% (18.05% × 6.69%) of the general population older than age 45, consistent with the observed prevalence of neovascular age-related macular degeneration in the total US population (1.20%) from Klein et al.21

SENSITIVITY ANALYSIS

Sensitive variables included the annual rate of CNV development in the first eye, the annual rates of CNV development in the second eye (both for years 1-3 and year 4 and later), severe vision loss from treated CNV (for years 1-3), and severe vision loss from untreated CNV (for years 1-3). The base-case values (generated when all variables are given their assumed values) of these variables led to prediction that 2.24% of the BSD population would be legally blind from CNV within 10 years. Changing the input variables listed above from 50% to 150% of their base-case values resulted in deviations in the proportion of the BSD population developing legal blindness within 10 years from its base-case value (2.24%) of greater than 90% to 110% (2.02%-2.46%). Figure 4 illustrates the results of the detailed sensitivity analysis for these variables and indicates

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Table 4. Impact of Interventions on the Average Percentage of Patients With BSD Who Live to Develop CNV or Visual Acuity of 20/200 or Worse*

<table>
<thead>
<tr>
<th>Develop CNV in 1 or 2 Eyes Within</th>
<th>Develop Legal Blindness Within</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 y 25 y</td>
<td>10 y 25 y</td>
</tr>
<tr>
<td>Natural history</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td>Current laser treatment</td>
<td>12.4 16.6</td>
</tr>
<tr>
<td>Current laser treatment and 10% prophylaxis to Both eyes</td>
<td>11.2 15.1</td>
</tr>
<tr>
<td>Current laser treatment and 25% prophylaxis to Both eyes</td>
<td>9.5 12.8</td>
</tr>
<tr>
<td>Current laser treatment and 33% prophylaxis to Both eyes</td>
<td>8.5 11.5</td>
</tr>
<tr>
<td>Current laser treatment and 50% prophylaxis to Both eyes</td>
<td>6.4 8.8</td>
</tr>
<tr>
<td>Current laser treatment and 10% prophylaxis to Second eye only</td>
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<tr>
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<tr>
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</tr>
</tbody>
</table>

* BSD indicates bilateral soft drusen; CNV, choroidal neovascularization.
that the rate of legal blindness is most sensitive to the annual rate of CNV development in the first eye. None of the challenges to the model’s assumptions substantially altered the proportionate impact of preventive treatment. In all cases, the addition of a 10% effective preventive treatment applied bilaterally to patients with BSD was incrementally at least as effective in the prevention of legal blindness as the impact of current laser therapy.

Similar results were obtained when altering the base-case assumptions about clinical frequency of lesion types and treatment eligibility. When we altered our assumptions to reflect the lesion distribution and 13% treatment eligibility of the study by Freund et al, we found no change in the incremental percentage decrease produced by the addition of preventive treatment in the proportion of patients with BSD developing severe vision loss.

**COMMENT**

This model clarifies many issues of interest: the long-term natural history of patients with bilateral soft drusen, the long-term impact of current treatment on the prognosis of the high-risk patient, and the potential impact of prophylaxis.

The natural history of patients with BSD has never been formally observed past a period of 5 years. Therefore, it is of value to extrapolate the observed rates using reasonable assumptions. The assumptions made for this model are based on the available literature on age-related macular degeneration and produce valid results when compared with the best available population-based study of the incidence of CNV. For example, a rate of primary importance is the 1% development of CNV per eye per year among first eyes in the BSD population. This rate, which was extrapolated from a small, specialty-clinic based study by Smiddy and Fine, yielded 5-year incidence rates very close to those observed in the independent population-based studies of Beaver Dam (8.10% vs 7.1%, respectively). Furthermore, the model produces an estimate of CNV prevalence consistent with the prevalence observed in Beaver Dam (1.21% vs 1.2%, respectively).

The projections of the model for the first 5 years, then, is consistent with the most up-to-date, independent population-based study. The model very conservatively estimates the events of the first 10 years by decreasing the primary risk of CNV development by 25% for years 6 through 10. The outcomes occurring within 25 years include a 50% decrease in the primary risk of CNV development. These decreases were made because of our assumption that there is higher resistance to disease progression in patients who are short-term “survivors” of the risk of CNV and our desire not to overstate the risks facing the BSD population.

The model predicts that nearly 13% of patients with BSD can expect to develop CNV within 10 years. Clinicians should strongly encourage regular examinations for patients at high risk. This advice may be particularly relevant to patients with BSD younger than 65 years. The patient who is unfortunate enough to develop soft drusen at a young age would face a higher lifetime risk of CNV than one who only develops those high-risk characteristics in their 70s or 80s. Results from follow-up of patients with unilateral CNV support the dependence of risk only on time and not on patient age.

The model was also used to examine the potential incremental benefits of prophylaxis compared with our current regimen of laser treatment alone. A 10% effective prophylaxis given to both eyes of patients with BSD doubles the current impact on prevention of CNV-induced legal blindness provided by laser treatment by decreasing the 10-year incidence by 16.96% (from 2.24%-1.86%). A 33% effective prophylaxis (which is still only a modestly effective treatment) could more than halve the proportion of patients with BSD developing legal blindness within 10 years.

Any effective prophylaxis may be expensive to apply to the large numbers of patients with BSD. Applying prophylactic treatment to only the unaffected eye of patients with unilateral CNV is appealing since there would be less than one tenth as many people to treat (Ronald Klein, MD, written communication, September 1, 1996). However, the 10-year incidence of legal blindness with current treatment is 2.24%; with early preventive treatment (delivered to both eyes), this decreases to 1.86%, and with late preventive treatment (applied to second eye only), it decreases only to 2.06%. Of note, the additional 0.2% of patients with BSD avoiding legal blindness represents thousands of people.

There are major ongoing efforts to identify preventive interventions for people at high risk of exudative age-related macular degeneration. The National Eye Institute’s Age Related Eye Disease Study involving 4600 patients is investigating the possibly protective effects of antioxidant vitamins and zinc. Investigators from around the world are examining the effects of light laser photo-coagulation on the reduction of drusen and the development of CNV. Yet, preventive treatments do not have
to be as effective as panretinal photocoagulation for diabetic retinopathy, to have a major impact on blindness in the United States. The model shows that even small effects could have a major impact, verifying that efforts at prevention are well founded.

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REFERENCES


MELANOMA RESEARCH

Occurrence of Cutaneous and Uveal Melanoma in Patients With Uveal Melanoma and Their First-Degree Relatives

Uveal and cutaneous melanomas are rare tumors, but have been described to occur together in one patient or in members of the same family. A group of 109 consecutive uveal melanoma patients from one specialized ocular tumor clinic were investigated dermatologically. The patient’s own history and medical data and the family history of skin or eye problems were recorded. A total of three cutaneous melanomas were found as a result of this study—two in ocular melanoma patients and one in a first-degree relative. Four patients had first-degree relatives with a skin melanoma (in three of these families dysplastic naevus syndrome was also found), and one patient had a first-degree relative with an uveal melanoma. To find cutaneous and uveal melanoma coexisting in two cases and cutaneous melanoma in first-degree relatives in four cases out of a total of 109 uveal melanoma patients seems more than a coincidence. A linking factor in three cases was the familial atypical multiple mole melanoma syndrome, suggesting a common genetic predisposition to both malignancies in these families. In our only family with familial uveal melanoma, cutaneous melanoma and typical naevi did not occur. A different genetic mechanism for these cases is probable.

(1998;8:175-180) C. L. M. van Hees et al, Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands