Intravitreal Bevacizumab for Subfoveal Choroidal Neovascularization Associated with Pattern Dystrophy

Maurizio Battaglia Parodi,1 Pierluigi Iacono,2 Marialucia Cascavilla,1 Ilaria Zucchiatti,1 Dimitrios Stylianos Kontadakis,1 and Francesco Bandello1

PURPOSE. To assess the effects of intravitreal bevacizumab injections in the treatment of subfoveal choroidal neovascularization (CNV) associated with pattern dystrophy (PD) of the retinal pigment epithelium.

METHODS. The study was a prospective, nonrandomized, open-label, interventional clinical trial in which 12 patients were prospectively enrolled. Patients with a diagnosis of PD complicated by subfoveal CNV were considered for the study. All patients underwent a complete ophthalmic examination, including ETDRS visual acuity measurement, electroretinogram, electrocochleogram, optical coherence tomography, and fluorescein angiography. The treatment protocol began with a loading dose of three consecutive injections at 1-month intervals, followed by injections administered as needed, according to OCT parameters and angiographic features observed during a 24-month follow-up period. The number of eyes with a visual acuity loss of fewer than 15 letters (<3 ETDRS lines), compared with baseline measures, was recorded at the 6-, 12-, and 24-month examinations.

RESULTS. Twelve patients completed the planned visits and were included in the study. A visual acuity loss of fewer than 15 letters was not registered in any case at the 6- and 12-month examinations and was found in only one (8%) patient at the 24-month examination. The mean best corrected visual acuity (BCVA) and the mean central macular thickness (CMT) at baseline were 0.73 ± 0.54 (logMAR ± SD) and 276 ± 95 µm (SD), respectively. At the 3-month examination, the mean BCVA significantly improved to 0.48 ± 0.27, whereas the mean CMT decreased to 220 ± 71 µm. At the 12-month examination, the mean BCVA was 0.45 ± 0.24, and the mean CMT was 209 ± 53 µm. At the 24-month (last) follow-up, the BCVA showed substantial stabilization and the CMT decreased to 199 ± 34 µm. No side effects or complications were registered.

CONCLUSIONS. Intravitreal bevacizumab injection is a beneficial treatment for subfoveal CNV associated with PD. Further studies are warranted to confirm these initial results and to analyze the morphofunctional changes during the follow-up. (ClinicalTrials.gov number, NCT00391144.) (Invest Ophthalmol Vis Sci. 2010;51:4358–4361) DOI:10.1167/iovs.10-5237

Pattern dystrophy (PD) of the retinal pigment epithelium (RPE) is a heterogeneous group of inherited retinal diseases. Each entity is characterized by specific RPE alterations, and several forms have been identified, including adult-onset foveomacular vitelliform dystrophy (AOFVD), butterfly-shaped pigment dystrophy, reticular dystrophy (RD), and PD simulating fundus flavimaculatus and fundus pulverulentus.1,2 Usually, visual function is preserved for a long time. Nevertheless, the development of atrophic changes or choroidal neovascularization (CNV) can lead to progressive deterioration of visual acuity.1–5 The treatment of PD-related CNV is still controversial. In the short term, photodynamic therapy with verteporfin can stabilize the visual function in eyes with subfoveal CNV, but it is unable to guarantee a good visual prognosis in the long-term.6,7 The purpose of this prospective investigation was to assess the effects of intravitreal bevacizumab injections (IVBIs) in the treatment of subfoveal CNV associated with PD over a 24-month follow-up period.

METHODS

The present trial study was a prospective, nonrandomized, open-label, interventional pilot study conducted in patients affected by subfoveal CNV secondary to PD. The design of the study was approved by the local institutional review board. Written informed consent was obtained from all patients after an extensive explanation of the purpose of the study. The research adhered to the tenets of the Declaration of Helsinki.

Beginning in July 2006, patients affected by PD associated with subfoveal CNV were prospectively enrolled. Inclusion criteria were a diagnosis of PD, identification of subfoveal CNV showing classic or occult characteristics, best corrected visual acuity (BCVA) of at least 20/200 evaluated on ETDRS charts (corresponding to a 35-letter ETDRS score), and availability to sign a written informed consent.

Exclusion criteria were the presence of other ocular disorders that might affect the clinical assessment, previous photodynamic therapy with verteporfin, inability to attend for the scheduled visits, pregnancy, peripheral vascular disease, thromboembolism or stroke, intraocular surgery within the past 2 months, or capsulotomy in the study eye within the past month.

The diagnosis of PD was based on the detection of typical retinal RPE alterations, in patients younger than 55 years, the identification of other family members affected by the disease, and the registration of a normal electroretinogram (ERG) with a normal or subnormal electrocochleogram (EOG).

Each patient underwent an ophthalmic examination with BCVA on standard ETDRS logMAR charts, an anterior segment slit lamp examination, tonometry, dilated fundus biomicroscopy, ERG, EOG, optical coherence tomography (OCT), and fluorescein angiography (FA). The ERG and EOG were recorded according to ISCEV recommendations.
FA was performed with a retinal angiograph (HRA 2; Heidelberg Engineering, Heidelberg, Germany). An OCT examination was performed (Stratus OCT; Carl Zeiss Meditec, Dublin, CA), with the fast macular thickness map protocol, consisting of six 6-mm radial lines (oriented 30° apart) used in all scans. The central 1-mm thickness of the retinal map analysis protocol was recorded for central retinal calculations. In cases in which the automatic segmentation algorithm of the fast macular thickness map failed to identify inner and outer retinal boundaries correctly, the central macular thickness (CMT) was manually measured for each radial scan, and the average of the six values was used for statistical analysis.

Over the 24 months of the follow-up period, a complete ophthalmic examination was repeated monthly. A BCVA assessment was performed at each visit by an ophthalmologist masked to the patient’s treatment. An intravitreal injection of bevacizumab 1.25 mg (Avastin; Genentech, South San Francisco, CA) was administered in the operating theater under sterile conditions. The injection was performed 3.5 to 4.0 mm posterior to the corneal limbus with a 30-gauge needle after topical anesthesia. The injection site was compressed with a sterile cotton swab to avoid reflux when removing the needle. After a loading phase of three injections at 1-month intervals, further retreatments were administered on the basis of the detection of any type of fluid on OCT and/or when FA examination revealed CNV leakage. The main outcome measure was the number of eyes with a 15-letter loss (<3 ETDRS lines) at the 6-, 12-, and 24-month examinations compared with baseline values. Secondary outcomes included OCT changes over the follow-up.

Statistical analyses were performed with Student’s t-test. Differences at P < 0.05 were statistically significant (SPSS ver. 14.0; SPSS, Chicago, IL).

RESULTS

Twenty patients affected by subfoveal CNV related to PD were considered for the study, but eight (40%) patients were excluded because of low BCVA. Overall, 12 patients fully satisfied the inclusion and exclusion criteria.

The median age of the patients (six women and six men) was 53.5 years (mean age at baseline, 54.5 ± 5.5; range, 46–63). Ten patients had a diagnosis of reticular dystrophy, and two were affected by adult-onset foveomacular vitelliform dystrophy.

The mean time between the onset of symptoms (visual loss and/or distortion) and the diagnosis of CNV secondary to PD was 11.5 ± 3.5 days (range, 5–17). Table 1 shows the mean changes in the BCVA at 6, 12, and 24 months of follow-up. A visual acuity loss worse than 15 letters was registered in 95% CI, 95% confidence interval.

Table 1. Visual Acuity Changes during the 24 Months of Follow-up

<table>
<thead>
<tr>
<th>Change Lines</th>
<th>6 mo</th>
<th>12 mo</th>
<th>24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3</td>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>≥1</td>
<td>12</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>≤−1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>≤−3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Fifty percent of the patients showed a visual acuity gain of 3 lines at the 6-month examination, and all patients gained at least 1 line. At the 12- and 24-month examinations, 92% and 58% of the patients improved by 1 and 3 lines, respectively. At the final visit, only one patient had a loss of 1 line in BCVA, in comparison with the baseline value.
by at least 3 lines, two gained 3 lines, one gained 4 lines, and two and one gained 5 and 6 lines, respectively. At the 12-month examination, the mean BCVA decreased to 220 ± 53 \( \text{Snellen equivalent} \) and 276 ± 95 \( \mu \text{m} \) (SD), respectively. At the 3-month examination, the mean BCVA improved to 0.48 ± 0.27 \( \text{(logMAR} \pm \text{SD}; \sim 20/100 \text{Snellen equivalent}) \) and CMT decreased to 220 ± 71 \( \mu \text{m} \). Subsequently, at the 6- and 12-month examinations, a substantial stabilization of the mean BCVA was observed; the mean CMT was 215 ± 47 and 209 ± 53 \( \mu \text{m} \), respectively. At the final visit, the mean BCVA showed an improvement of 2.8 lines in comparison with the baseline value. The mean CMT decreased to 199 ± 34 \( \mu \text{m} \) with a final reduction of 28\% compared with the baseline value. Statistical analysis revealed that both BCVA and CMT significantly improved from the third month on.

After the loading phase of three consecutive IVBIs, nine (75\%) eyes reached a CNV stabilization, confirmed by means of FA and OCT and did not require additional injections during the subsequent follow-up (Fig. 1). On the contrary, three eyes showed a CNV progression, requiring seven and eight IVBIs in one and two eyes, respectively. It is noteworthy that the three patients requiring additional injections during the follow-up showed a meaningful BCVA improvement at the 24-month visit. The supplementary injections were necessary to stabilize CNV progression. Specific details on CMT and BCVA changes over the follow-up are listed in Table 3. The mean number of IVBIs was 4.0 at the end of 12 months and 4.2 at the end of the 24 months.

No side effects or complications were registered during the follow-up period.

**DISCUSSION**

PD is a heterogeneous group of retinal disorders natural histories that are not entirely known. The prognosis is generally favorable, if the course is not complicated by the development of macular atrophy or CNV.\(^1\)–\(^5\) Visual function is often stable during short-term follow-up in cases presenting subfoveal CNV, but tends to decline in the long-term.\(^1\)–\(^5\) PD is an infrequently occurring disease, and there are no precise data about the prevalence of CNV occurrence. Nevertheless, a recent case series reported that half of the patients had a disciform scar in the fellow eye with consequent low vision,\(^6\) and 40\% of cases examined for the current investigation were excluded because of BCVA \(<20/200\). These findings suggest that visual function can be severely impaired by the occurrence of CNV in PD. Possible options for subfoveal CNV associated with PD include laser photocoagulation, photodynamic therapy (PDT), surgical removal, and anti-VEGF therapy.

The unexpected enlargement of the scar after laser photocoagulation of an extrafoveal CNV secondary to fundus flavomaculatus suggests that the RPE may be irreversibly damaged by the thermal insult,\(^6\) and laser treatment may therefore be harmful in this and similar disorders.

PDT has been used to treat PD-related subfoveal CNV. This approach provides transitory functional stabilization,\(^6\) which is followed by a progressive deterioration in the long-term.\(^7\) More specifically, a decrease of at least 3 lines was registered in 70\% of cases at the 3-year examination.\(^7\) No information is currently available regarding surgical removal of CNV associated with PD. Last, only a single report describes a case of adult-onset foveomacular vitelliform dystrophy associated with occult CNV treated with intravitreal bevacizumab, showing a decrease in subretinal fluid with no visual acuity improvement in the short-term.\(^9\)

In the absence of a proven therapy that improves or at least stabilizes visual function, we designed a prospective interventional study to evaluate the effect of IVBI in the treatment of subfoveal CNV secondary to PD on the basis of the positive

**Table 3.** CMT and BCVA Changes of the Three Patients Needing Additional Intravitreal Bevacizumab Injections over the Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 mo</th>
<th>2 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>9 mo</th>
<th>12 mo</th>
<th>18 mo</th>
<th>24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>CMT</td>
<td>415</td>
<td>331</td>
<td>323</td>
<td>349</td>
<td>290</td>
<td>382</td>
<td>283</td>
<td>231</td>
</tr>
<tr>
<td></td>
<td>BCVA</td>
<td>0.6</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.6</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Case 2</td>
<td>CMT</td>
<td>330</td>
<td>226</td>
<td>265</td>
<td>302</td>
<td>310</td>
<td>312</td>
<td>300</td>
<td>221</td>
</tr>
<tr>
<td></td>
<td>BCVA</td>
<td>1.0</td>
<td>0.9</td>
<td>1.0</td>
<td>1.0</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Case 3</td>
<td>CMT</td>
<td>412</td>
<td>328</td>
<td>325</td>
<td>326</td>
<td>248</td>
<td>255</td>
<td>231</td>
<td>231</td>
</tr>
<tr>
<td></td>
<td>BCVA</td>
<td>1.0</td>
<td>0.5</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

A significant improvement in BCVA and CMT was also registered in the three patients who needed additional injections to stabilize the progression of CNV.
results obtained in other diseases. The results we achieved are encouraging. No patient showed a 15-letter loss over the 24-month follow-up. On the contrary, a BCVA improvement was attained in 92% of cases, with only a single eye losing 1 line over the 2-year follow-up. Moreover, OCT parameters paralleled with visual function, showing progressive normalization of macular thickness.

The mechanisms of this positive response are only speculative. We may hypothesize that the antiangiogenic therapy acts directly on the neovascular component, sparing the retinal cells. In particular, RPE cells are thought to be primarily impaired in PD with the accumulation of intracellular lipofuscin. N-retinylidine-N-retinylethanol-amine (A2-E) is a retinoid component of lipofuscin that seems to play an important role in the RPE cells dysfunction bringing about damage to the membrane integrity and phototoxicity. The effect of laser photocoagulation and PDT on RPE cells engulfed in lipofuscin may lead to greater impairment, with consequent apoptosis. On the contrary, therapy designed to block vascular endothelial growth factor, may preserve RPE cell viability. Interestingly, the mean number of IVBIs (4.2) was low over the follow-up period. This good response reflects the more favorable natural history of PD-related CNV with respect to other diseases, such as age-related macular degeneration.

We acknowledge that this study has several limitations. It is to be regarded as a pilot trial to ascertain the effects of a therapy based on repeated IVBIs for the treatment of subfoveal CNV secondary to PD. Major limitations include the small number of patients involved and the lack of a control group. However, both the infrequency of PD and the rarity of the neovascular complication may make these limitations inevitable. Thus, the planning of a randomized clinical trial in the future may be difficult. Moreover, according to the protocol, the treatment consisted of a loading phase of three IVBIs at 1-month intervals, with further treatments administered on the basis of OCT and/or FA results. It is possible that other treatment regimens would accomplish similar positive outcomes.

In essence, IVBI is a valuable treatment for subfoveal CNV associated with PD over a 2-year follow-up period. Further studies are needed to confirm our results and to assess the changes in other morphofunctional parameters, such as fundus autofluorescence and retinal sensitivity in correlation with IVBI.

References