Laser Photocoagulation, Photodynamic Therapy, and Intravitreal Bevacizumab for the Treatment of Juxtafoveal Choroidal Neovascularization Secondary to Pathologic Myopia

Maurizio Battaglia Parodi, MD; Pierluigi Iacono, MD; Alexandros Papayannis, MD; Saumil Sheth, MD; Francesco Bandello, MD

Objective: To compare the effects on visual acuity of laser treatment (LT), photodynamic therapy (PDT) with verteporfin, and intravitreal bevacizumab treatment in patients with juxtafoveal choroidal neovascularization secondary to pathologic myopia.

Methods: This prospective randomized clinical investigation enrolled 54 patients, who were divided into 3 groups receiving PDT, LT, or intravitreal bevacizumab treatment. The anti–vascular endothelial growth factor group received 1.25 mg of intravitreal bevacizumab at baseline; retreatment was performed if persistent intraretinal or subretinal fluid evaluated on optical coherence tomography or if choroidal neovascularization progression was detected on fluorescein angiography. The PDT group received treatment following the Verteporfin in Photodynamic Therapy Study Group guidelines. The LT group was submitted to direct LT and received PDT treatment if subfoveal recurrence or progression was detected on fluorescein angiography. A change in best-corrected visual acuity was the primary outcome.

Results: The mean best-corrected visual acuity in the PDT group decreased from 0.52 logMAR (SD, 0.24 logMAR) at baseline to 0.72 logMAR (SD, 0.25 logMAR) at the end of the study (P=.002). The LT group showed substantial stabilization from mean baseline visual acuity (mean, 0.45 logMAR [SD, 0.27 logMAR]) to the 24-month (mean, 0.56 logMAR [SD, 0.34 logMAR]) examination values. The mean best-corrected visual acuity in the anti–vascular endothelial growth factor group increased from 0.6 logMAR (SD, 0.3 logMAR) at baseline to 0.42 logMAR (SD, 0.35 logMAR) at the end of the study (P=.006).

Conclusions: Overall, bevacizumab treatment offers the best functional results during a 2-year follow-up. In view of the small size of the sample in this study and the relatively low frequency of juxtafoveal choroidal neovascularization secondary to pathologic myopia, a multicentric clinical trial is necessary to validate our results.


PATHOLOGIC MYOPIA IS ONE OF the major causes of blindness, as blindness is legally defined, in many developed countries,1 with a prevalence of around 2% in the general population.2 It is characterized by an excessive extension of the eyeball associated with degenerative changes of the retina, choroid, and sclera. Posterior staphyloma, chorioretinal atrophy, and lacquer cracks in the Bruch membrane commonly occur.3 Choroidal neovascularization (CNV) is the most frequent vision-threatening macular complication clinically observed in pathologic myopia.4

The location of CNV with respect to the fovea can dictate the choice of treatment. Direct laser photocoagulation may still be considered a valid option when CNV is extrafoveal. On the other hand, subfoveal CNV rules out conventional laser treatment as a viable option and may benefit from photodynamic therapy (PDT) with verteporfin. Photodynamic therapy has been proven to reduce visual acuity deterioration at the 1-year follow-up, though no statistically significant effect was confirmed after 2 years.5,6 More recently, 2 large studies recorded positive results following the use of PDT in patients with nonsubfoveal myopic CNV. More specifically, Pece et al7 found that visual acuity was stabilized in patients with juxtafoveal CNV, while Virgili et al8 registered a positive outcome from the use of PDT in a retrospective study on a large series of patients with nonsubfoveal myopic CNV.
Promising results have been reported in the treatment of subfoveal CNV with systemic or intravitreal administration of bevacizumab, a full-length monoclonal antibody able to bind and inactivate all isoforms of vascular endothelial growth factor (VEGF), which plays an important role as a mediator of pathologic angiogenesis. The aim of the present randomized clinical pilot study comparing laser treatment (LT), PDT with verteporfin, and intravitreal bevacizumab injection therapy for myopic juxtafoveal CNV during a period of 24 months of follow-up was to identify the treatment that achieves the best visual acuity.

### METHODS

Patients referred to the departments of ophthalmology at the University of Udine and University of Trieste between January and July 2006 with diagnoses of juxtafoveal CNV in pathologic myopia were prospectively enrolled in the study. This research was approved by the local institutional review boards and adhered to the tenets of the Declaration of Helsinki. Each patient provided signed informed consent to the study.

Inclusion criteria were (1) CNV secondary to pathologic myopia, (2) classic, well-defined juxtafoveal CNV (1-200 µm from the foveal center) shown on fluorescein angiography (FA), (3) greatest linear dimension no larger than 5400 µm, (4) best-corrected visual acuity (BCVA) from 20/200 to 20/40 on an Early Treatment Diabetic Retinopathy chart, (5) duration of untreated CNV activity or progression.

Pathologic myopia was defined as an eye that required a distance correction of at least −6.0 diopters (spherical equivalent). An eye that had a spherical equivalent less myopic than −6.0 diopters was eligible if it had retinal abnormalities consistent with pathologic myopia (such as lacquer cracks, chorioretinal atrophy, posterior staphyloma, and atrophic patches) and if the axial length of the eye was at least 26.5 mm.

Exclusion criteria were (1) evidence of any condition other than pathologic myopia associated with CNV; (2) any significant ocular disease that had compromised or could compromise vision in the study eye; (3) active hepatitis; clinically significant liver disease, porphyria, or other porphyrin sensitivity; or pregnancy; (4) peripheral vascular disease, thromboembolism, or stroke; (5) intraocular surgery within the last 2 months or capsulotomy in the study eye within the last month; and (6) previous laser photocoagulation.

The recruited patients were divided into 3 subgroups: subjects who underwent PDT with verteporfin (PDT group); patients who underwent krypton laser photocoagulation of the juxtafoveal CNV (LT group); and patients who underwent intravitreal bevacizumab injection (bevacizumab group). Each patient was randomly allocated to 1 of the 3 treatment groups through a computer-generated number. Each patient underwent a complete ophthalmological assessment, including BCVA on standard Early Treatment Diabetic Retinopathy Study log-MAR charts at 4 m, slitlamp examination, tonometry, and dilated fundus examination.

Fluorescein angiography was carried out using Heidelberg Retinal Angiography. After the initial diagnosis, FA was repeated 1 day before the treatment (conventional laser or PDT treatment) and then, during the first year of follow-up, every 3 months in the PDT group and every month in the LT group. Fluorescein angiography was performed every 3 months in all groups during the following 12 months of follow-up.

After the randomization phase, the bevacizumab group underwent optical coherence tomography (OCT) examination with a Stratus OCT (Carl Zeiss Meditec, Dublin, California). Macular OCT was performed every month during follow-up.

All OCT scans were performed using the fast macular thickness map protocol, consisting of six 6-mm radial lines (arranged 30° apart). 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 foveal thickness was manually measured for each radial scan and the mean of the 6 values obtained was used for statistical analysis.

In the bevacizumab group, FA was performed every 3 months during the 24-month follow-up. At each scheduled examination, a complete ophthalmological assessment was carried out by an investigator who had had no previous contact with the subject and was unaware of the treatment previously administered. In the PDT group, the first and subsequent treatments were performed strictly following the Verteporfin in Photodynamic Therapy Study Group guidelines. Eyes in the LT group that developed recurrent CNV with subfoveal location during follow-up could be retreated using PDT.

Patients in the bevacizumab group received intravitreal injections in the operating room under sterile conditions. Intravitreal bevacizumab injection was performed 3.5 to 4.0 mm posterior to the corneal limbus using a 27-gauge needle after topical anesthesia. The injection site was compressed with a sterile cotton swab to avoid reflux when removing the needle. Additional intravitreal bevacizumab injections were administered when the OCT examination revealed persistent or recurrent intraretinal or subretinal fluid, or when FA examination revealed CNV activity or progression.

The main outcome measure was the postoperative change in visual acuity compared with the baseline examination in all subgroups. Mean BCVA and central foveal thickness at baseline and each follow-up examination were compared using the t test (paired or unpaired where appropriate; P < .05 was considered statistically significant).

Fifty-four patients affected by juxtafoveal CNV in pathologic myopia were recruited; 4 patients were excluded because they could not attend the scheduled examinations; 3 patients were not recruited because they were affected by media opacity. Thirty-seven patients were female and 17 male. Eighteen patients were randomized to PDT, 17 to LT, and 19 to intravitreal bevacizumab injection. Only patients attending the planned examination during the 24-month follow-up were considered in the study.

The demographic characteristics of the patients are outlined in Table 1. Mean age was 44.5 years in the LT group, 48.1 years in the PDT group, and 50.8 years in the bevacizumab group. No statistically significant differences were found among the 3 groups regarding age.

Table 2 shows mean BCVA in the 3 treatment arms during follow-up. At baseline, no statistically significant difference was registered among the 3 groups. At the 3- and 6-month follow-ups, a substantial stabilization of BCVA was observed in the LT and PDT groups, whereas a statistically significant improvement was recorded in the bevacizumab group. At the 9-month follow-up, mean BCVA significantly worsened to 0.67 logMAR in the PDT group (P < .05). At the same time, the LT group pre-
A best-corrected visual acuity shown no statistically significant difference among the 3 groups at baseline.

At baseline, no statistically significant difference was registered among the subgroups. From the 3-month examination, a statistically significant improvement of BCVA was recorded in the bevacizumab group. At the 1-year follow-up, the PDT group showed a worsening in BCVA, the laser treatment group maintained the baseline mean BCVA, whereas only the bevacizumab group showed a statistically significant BCVA improvement. At the 24-month examination, a worsening in BCVA was registered both in the PDT group (reaching statistically significant difference) and in the laser treatment group (without statistically significant difference), whereas the bevacizumab group retained its visual improvement.

From the 3-month examination, a statistically significant improvement in BCVA from baseline in the bevacizumab group from the 3-month examination on. Statistically significant worsening in BCVA from baseline in the PDT group from the 9-month examination on. Statistically significant difference favoring photocoagulation and intravitreal bevacizumab injection, instead of PDT treatment, was found at 9 and 12 months.

At the 18- and 24-month follow-up examinations, the bevacizumab group maintained its initial improvement in BCVA, with a final gain of 1.8 lines from the baseline value to the 24-month examination value. The LT group showed a stabilization of BCVA with respect to baseline values, with visual loss of 1.1 lines (not statistically significant), whereas mean BCVA decreased in the PDT group from 0.52 logMAR at baseline to 0.72 logMAR at the end of the study, with a statistically significant worsening of 2 lines. At the 24-month examination, only the bevacizumab group displayed a statistically significant difference compared with the PDT group, with a mean difference of 3 lines. Table 3 summarizes the BCVA changes after treatment in each subgroup. In the PDT, LT, and bevacizumab groups, 27.5%, 41%, and 79% of eyes, respectively, exhibited signs of stabilization or improvement in visual acuity. At the final examination, 5%, 30%, and 58% of eyes in the PDT, LT, and bevacizumab groups, respectively, displayed a BCVA better than 20/40. The bevacizumab group was the most likely to preserve the initial BCVA or gain Early Treatment Diabetic Retinopathy Study lines ($\chi^2$ test, $P = .005$).

During the first year of follow-up, CNV recurrence with subfoveal extension was registered in 9 eyes (53%) in the LT group, which were retreated using PDT in accordance with the study protocol (Table 3); a foveal extension developed in 13 eyes (72%) in the PDT group (Table 4). In the bevacizumab group, 4 patients revealed a CNV foveal extension. Overall, 80% of subfoveal CNV recurrence occurred during the first 6 months of follow-up. No subfoveal CNV recurrence was detected in the second year.

The mean number of PDT sessions (Table 4) was 2.3 and 0.6 in the PDT and LT groups, respectively, during the first year of follow-up. The mean number of PDT treatments within the following 12 months of follow-up was 1.2 in the PDT group and 0.5 in the LT group. Overall, at the 24-month examination, the mean number of PDT treatments in the LT group (mean, 1.17 [SD, 0.68]}
1.18) turned out to be lower than the mean number of PDT retreatments (mean, 2.55 [SD, 1.19]; total PDT administration excluded the first PDT treatment) in the PDT group, the difference being statistically significant (P = .002). At the 24-month examination, the mean number of intravitreal bevacizumab injections was 3.8 (SD, 2.5; range, 1-11); only 4 patients required additional intravitreal bevacizumab injections during the second year.

Mean central foveal thickness measured by OCT improved from 234 µm at baseline to 201 µm at the 1-month examination; this reduction was preserved after 6 months and increased slightly to 226 µm at the 12-month examination. In the second year, the assessment of central foveal thickness revealed a stabilization, with a final mean value of 221 µm. At each scheduled examination, mean differences compared with baseline were not statistically significant.

At the 1-month examination, the mean laser scar area was 3.03 mm² (SD, 1.30 mm²); at the final test, the mean laser scar area extended up to 5.21 mm² (SD, 2.45 mm²), an increase of 72%. In all cases, the enlargement of the atrophic laser scar after laser treatment did not involve the foveal area. During follow-up, no systemic or adverse ocular event—endophthalmitis, cataract, glaucoma, intraocular inflammation, or retinal detachment—was registered.

Choroidal neovascularization is the most frequent vision-threatening complication in pathologic myopia. Clinical and histopathological studies have recorded the presence of CNV in 4% to 11% of highly myopic eyes. Moreover, studies providing long-term follow-up have demonstrated that there is a progressive decline in visual acuity in eyes with myopic CNV, especially in older patients.

During the past 3 decades, laser photocoagulation has been the only effective means of treating nonsubfoveal CNV associated with pathologic myopia, but with the advent of PDT, some authors have suggested that PDT could also achieve positive results. Other treatments such as submacular surgery or macular translocation have not gained in popularity because their effectiveness has never been demonstrated in large randomized controlled studies and because of safety concerns.

Although beneficial for subfoveal myopic CNV, PDT with verteporfin at present has no precise indication for nonsubfoveal CNV. More recently, anti-VEGF therapy has been used for the treatment of subfoveal CNV secondary to pathologic myopia, and the preliminary results in a short-term follow-up seem promising. Other treatments such as submacular surgery or macular translocation have not gained in popularity because their effectiveness has never been demonstrated in large randomized controlled studies and because of safety concerns.

In the largest published study, laser photocoagulation of CNV from 100 to 400 µm from the foveal avascular zone center was retrospectively compared with observation. More specifically, 50 eyes treated with photocoagulation were compared with 50 controls. A significant difference in favor of photocoagulation was registered at 2 years, but no difference between the 2 groups was found at 5 years. At the end of follow-up, 100% of untreated patients and 72% of treated patients had a subfoveal extension and a subfoveal recurrence, respectively. Similar results were reported by Ruiz-Moreno et al; the initial visual improvement that had appeared at

**Table 3. Frequency of Mean Changes in Best-Corrected Visual Acuity From Baseline to the 24-Month Examination**

<table>
<thead>
<tr>
<th>Group</th>
<th>&lt;−3</th>
<th>&lt;−1</th>
<th>0</th>
<th>&gt;1</th>
<th>&gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photodynamic therapy</td>
<td>8 (44)</td>
<td>13 (72)</td>
<td>1 (5.5)</td>
<td>4 (22)</td>
<td>1 (5.5)</td>
</tr>
<tr>
<td>Laser treatment</td>
<td>7 (41)</td>
<td>10 (59)</td>
<td>1 (6)</td>
<td>6 (35)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Intravitreal bevacizumab</td>
<td>1 (5)</td>
<td>4 (21)</td>
<td>2 (11)</td>
<td>13 (68)</td>
<td>7 (36)</td>
</tr>
</tbody>
</table>

*Stabilization or improvement of best-corrected visual acuity was registered in 27.5%, 41%, and 79% of the photodynamic therapy, laser treatment, and bevacizumab groups, respectively.*

**Table 4. PDT Sessions and Foveal Extension of Juxtafoveal Choroidal Neovascularization**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Laser Treatment</th>
<th>PDT</th>
<th>Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean No. of PDT sessions</td>
<td>0.6</td>
<td>2.3</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Foveal extension, No. (%)</td>
<td>9 (53)</td>
<td>13 (72)</td>
<td>4 (21)</td>
</tr>
</tbody>
</table>

**12-Month Examination**

| Mean No. of PDT sessions | 0.5 | 1.2 | Not applicable |
| Foveal extension, No. (%) | 0 | 0 | 0 |

**24-Month Examination**

*Abbreviation: PDT, photodynamic therapy.*

*During the first year, choroidal neovascularization recurrence with subfoveal extension was registered in 9 eyes (53%) in the laser treatment group. A foveal extension developed in 13 eyes (72%) of the photodynamic therapy group. Four patients showed choroidal neovascularization foveal extension in the bevacizumab group. No subfoveal choroidal neovascularization recurrence was detected during the second year.*
the 1- and 2-year follow-ups was subsequently lost at the 3-year examination.

Bottoni and Tilanus performed a retrospective, observational study on 9 patients with juxtafoveal CNV, with a mean follow-up of 5.8 years. Final visual acuity was 20/40 in 77% of the cases, but unfortunately the authors did not report the baseline visual acuity values, making the interpretation of these data difficult. Hayashi et al present similar results in 11 eyes with juxtafoveal CNV. After a follow-up of 5 years, 5 eyes had final visual acuities greater than 5/10 (45%), 2 eyes had visual acuities from 1/10 to 5/10, and 4 eyes exhibited visual acuities of less than 1/10.

The past few years have seen preliminary results published concerning the use of PDT in the treatment of myopic juxtafoveal CNV. Cohen et al have described favorable results of PDT in 3 patients with juxtafoveal CNV associated with pathologic myopia, with a final visual acuity greater than 20/25 and a single PDT session. In a series of 11 patients, Lam et al reported stable or improved final visual acuity in all cases, with a mean change in BCVA of 0.57 to 0.39 logMAR at the 1-year follow-up examination.

More recently, Virgili et al recorded a positive outcome of PDT in a retrospective study of a large series of patients with nonsubfoveal myopic CNV. Unfortunately, the authors did not specify the visual acuity values associated with the 28 juxtafoveal CNV cases, rendering the comparison with our data impossible.

Pec et al have described the results of a prospective interventional case series performed on a large series of patients with juxtafoveal CNV who were treated with PDT and followed up for 32 months (range, 12-56 months). A total of 48 patients were split into 2 groups by age, with the cutoff set at 55 years. The final visual acuity was mostly stable in the subjects younger than 55 years (27 patients) compared with baseline visual function (0.37 vs 0.41 logMAR), whereas it was considerably lower in the group older than 55 years (22 patients), though this was not statistically significant (0.31 vs 0.72 logMAR). It is hard to make a precise appraisal of these results owing to a certain imprecision in the data (Table 2 and Table 3).

The results of the current investigation indicate that BCVA statistically improved in the bevacizumab group, while it worsened in the PDT group, at both the 12- and 24-month examinations. Best-corrected visual acuity was stable in the LT group during the 2-year follow-up. At the final examination, 5%, 30%, and 58% of eyes in the PDT, LT, and bevacizumab groups, respectively, showed a BCVA better than 20/40. Moreover, 53% of eyes in the LT group, 72% of eyes in the PDT group, and 21% of eyes in the bevacizumab group showed recurrent subfoveal CNV during the 2 years of follow-up.

Overall, our results show that treatment with bevacizumab offers the best functional results during a 2-year follow-up. Bearing in mind the available data regarding intravitreal bevacizumab, information on myopic juxtafoveal CNV remains limited. Chan et al have described 2 eyes with juxtafoveal CNV secondary to pathologic myopia that underwent 3 injections at monthly intervals, recording a visual acuity improvement with fibrotic evolution of juxtafoveal CNV at the 6-month examination. Sakaguchi et al have discussed 2 eyes affected by myopic juxtafoveal CNV that obtained a functional and angiographic improvement after a single bevacizumab injection at the 4-month examination. The study by Gharbiya et al also included subfoveal and juxtafoveal CNV; unfortunately they did not provide separate results for each subtype of CNV.

Interestingly, the central foveal thickness decreased from 234 μm at baseline to 221 μm at the 24-month examination without reaching a statistically significant difference. Another study has already described the absence of a statistically significant difference in the reduction of central foveal thickness after intravitreal bevacizumab injection in the treatment of myopic CNV. This OCT feature seems to be a characteristic finding of myopic CNV, which generally shows a mild degree of exudation. We should also bear in mind that myopic juxtafoveal CNV and consequently the central foveal thickness did not represent the retinal thickness and the CNV lesion; more often the OCT radial scan crossed only the retinal component.

We are aware that our study has several limitations. First, it has no control group; however, considering the poor natural history of juxtafoveal CNV related to pathologic myopia, we consider a simple observation of the patient when he has already experienced a visual acuity deterioration to be unethical; second, the number of patients for each arm of the study is small owing to the difficulty in enrolling patients with myopic juxtafoveal CNV; third, the follow-up was relatively short. Indeed, given that the natural course of myopic CNV may be slow, a long-term follow-up with a greater number of subjects is necessary to assess the best therapeutic approach for myopic juxtafoveal CNV. In essence, this pilot randomized clinical trial designed to compare the effectiveness of PDT, LT, and bevacizumab in patients affected by myopic juxtafoveal CNV shows that intravitreal bevacizumab injection offers the best functional outcome during a 2-year follow-up.

Submitted for Publication: May 13, 2009; final revision received August 11, 2009; accepted September 12, 2009. Published Online: February 8, 2010 (doi:10.1001/archophthalmol.2009.408).

Correspondence: Francesco Bandello, MD, Department of Ophthalmology, University of Udine, Piazzale S. Maria Della Misericordia, Udine, Italy (francesco.bandello@uniud.it).

Financial Disclosure: None reported.

REFERENCES

5. Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of sub-


