Intravitreal Bevacizumab for Subfoveal Idiopathic Choroidal Neovascularization

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Objectives: To evaluate the short-term visual and anatomical outcomes and safety of intravitreal bevacizumab in subfoveal idiopathic choroidal neovascularization.

Methods: Thirty-two eyes of 32 patients with idiopathic choroidal neovascularization received intravitreal bevacizumab (1.25 mg/0.05 mL) in this prospective, noncomparative, interventional case series. Injection was repeated if optical coherence tomography showed intraretinal edema, subretinal fluid, and/or pigment epithelial detachment at a 4-week interval. Ophthalmic evaluations included best-corrected visual acuity, optical coherence tomography, and fundus fluorescein angiography. Patients were followed up for at least 12 weeks.

Results: The mean follow-up period was 4.2 months. At 12 weeks, the mean best-corrected visual acuity improved from 20/133 (median, 20/200) to 20/50 (median, 20/40) \((P < .001)\). The mean central macular thickness was reduced from 314.37 \(\mu\)m to 236.84 \(\mu\)m \((P < .001)\). At the final visit, 19 eyes (59%) had an improvement of best-corrected visual acuity of 3 or more lines, 11 eyes (34%) remained stable, and 2 eyes (6%) lost 3 or more lines. No significant ocular or systemic adverse effects were observed.

Conclusions: Short-term results suggest that intravitreal bevacizumab is safe and well tolerated in idiopathic choroidal neovascularization. Many patients showed marked improvement in visual acuity and a decrease in central macular thickness. Further evaluation with longer follow-up is needed to confirm long-term efficacy and safety.

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In patients aged 50 years or younger, choroidal neovascularization (CNV) develops secondary to some predisposing conditions such as pathological myopia, angioid streak, trauma, or inflammation (such as ocular histoplasmosis syndrome).1 In a significant number of young patients with CNV, no apparent cause can be detected, constituting idiopathic CNV (ICNV).2 These membranes are usually unilateral and final visual outcomes are considered to be more favorable than CNV due to age-related macular degeneration (AMD).3

Unlike AMD, sparse information exists on the natural course and treatment of subfoveal ICNV. Photodynamic therapy (PDT) has been shown to be effective in ICNV in many studies.4 Visual results with other treatment modalities in the form of transpupillary thermotherapy6 and submacular surgery or macular translocation are not satisfactory.7 Most of the published studies report low patient numbers with variable visual results.

The high expenses of PDT limit the number of treatments centers, particularly in developing countries. The visual results of PDT are inconsistent and highly variable. For example, in the study by Lam et al,9 visual improvement of 1 or more lines was seen in 25% of cases only, whereas Spaide et al10 reported 3 or more lines of improvement in 62.5% of cases in their small series. Encouraged by the preliminary findings of the ranibizumab trials in patients with AMD and subfoveal lesions, many physicians began to investigate a related compound, bevacizumab (Avastin; Genentech, Inc, South San Francisco, California), as a treatment for neovascular AMD with encouraging short-term effects in selected patients.11-13 In this study (the Bevacizumab for Idiopathic choroidal Neovascularization [BIN] study), we report short-term results of intravitreal bevacizumab for subfoveal ICNV in 32 consecutive patients, with a minimum follow-up of 12 weeks (range, 3-7 months).

METHODS

The BIN study was a prospective, noncomparative, consecutive, interventional study to...
evaluate the short-term visual and anatomical outcomes and safety of intravitreal bevacizumab in patients with ICNV involving the center of the foveal avascular zone. The study was reviewed and cleared by the institute review committee.

PATIENT SELECTION

Thirty-five patients with ICNV were approached, and 32 of them participated in the study. Three patients were previously treated with a single session of PDT with minimal response. One patient underwent PDT 4 months before joining the study, and 2 patients underwent PDT 3 months before joining. All of the other patients either refused or could not afford PDT.

Informed consent was obtained from each patient after explaining the potential ocular and systemic risks and benefits. Inclusion criteria included patients aged 50 years or younger with ICNV and optical coherence tomography (OCT) showing intraretinal edema, subretinal fluid (SRF), or pigment epithelial detachment (PED). Patients having features of choroiditis, myopic fundus changes, angiod streak, history of trauma, hereditary ocular diseases, or any other secondary causes of CNV were excluded from the study. Hypertension and history of a thromboembolic event were ruled out before inclusion in the study.

All of the patients were followed up for a minimum of 12 weeks. Before treatment, a full ophthalmological examination was done. Best-corrected visual acuity (BCVA) was recorded with the standard Snellen chart. Color fundus photography, fundus fluorescein angiography (FFA), and fast macular scan and line scan by OCT (Stratus OCT; Carl Zeiss Meditec, Dublin, California) were done before the start of treatment. Optical coherence tomography was repeated at 4 weeks and FFA at a 12-week interval. Using OCT, central macular thickness (CMT) (thickness of the 1-mm central retina using fast macular scan) and macular volume (MV) were measured. Blood pressure was checked before each injection and at days 1 and 7 after each injection.

INTRAVITREAL BEVACIZUMAB INJECTION AND FOLLOW-UP ASSESSMENT

A 0.2-mL aliquot of commercially available bevacizumab (25 mg/mL) was prepared for each patient in the oculair pharmacology and pharmacy department at our center and was stored at 4°C to 8°C. Two drops of proparacaine hydrochloride (0.5%) were instilled in the eye to be treated before the procedure. After preparing the eye with 5% povidone iodine, 1.25 mg/0.05 mL of bevacizumab was injected intravitreally through the pars plana using a 26-gauge needle. After the injection, intraocular pressure was checked digitally. An eye pad was placed after instilling 1 drop of 0.3% gatifloxacin. Patients were instructed to remove the eye pad after 3 to 4 hours and commence instillation of topical gatifloxacin (0.3%) 4 times daily for the next 4 days. Patients were seen on the following day to look for any complication and then at 1 and 4 weeks. At each visit, a full ophthalmological examination including BCVA, fundus photography, and OCT was done. Blood pressure was also checked.

Intravitreal injection was repeated if OCT showed persistent intraretinal edema, SRF, and/or PED. Fundus fluorescein angiography was performed at 12 weeks’ follow-up.

Central macular thickness was assessed by OCT using fast macular scan. In each image, automatic boundary lines for retinal thickness measurement were checked for any errors. In cases where gross error was seen, manual measurement was done using OCT electronic calipers. Macular volume was noted when available.

OUTCOME MEASURES

The primary outcome was the proportion of eyes that had improvement of vision (gain of ≥3 lines), were stable (within 2 lines), or had moderate vision loss (loss of ≥3 lines) at 12 weeks’ follow-up. Other outcome measures were change in the mean BCVA, CMT, and MV, requirement of retreatment, and adverse effects.

STATISTICAL ANALYSIS

Snellen visual acuity was converted to logarithm of minimum angle of resolution (logMAR) equivalents. For data analysis, STATA statistical software version 9.0 (Stata Corp, College Station, Texas) was used. Data were expressed as mean ± SD and median (range). Visual and OCT parameters were compared at baseline and 4, 8, and 12 weeks. Wilcoxon signed rank test was used for comparison of data that were not normally distributed, and paired t test was used for normally distributed data. In this study, P < .05 was considered statistically significant.

RESULTS

From December 2, 2005, to April 28, 2006, 32 eyes of 32 consecutive patients with ICNV were included in the study. There were 23 male patients (72%) and 9 female patients (28%). All of the patients were Asian Indian in origin. The mean age of the patients was 35.8 years, with a range of 18 to 50 years. All of the patients had a normal fundus in the fellow eye except 2 patients who had macular scars consistent with ICNV.

Snellen BCVA at baseline ranged from counting fingers at 2 feet to 20/40, with a median of 20/200. The mean ± SD logMAR BCVA before treatment was 1.02 ± 0.49 (20/210 in Snellen equivalents). Among the OCT parameters at baseline, the mean ± SD CMT was 314.37 ± 140.58 µm. The mean ± SD MV was 6.99 ± 0.82 µL (n = 22). In all cases, FFA demonstrated either classic or predominantly classic subfoveal CNV. The patients were followed up for a mean of 4.2 months (range, 3–7 months) and all completed 12 weeks of follow-up.

VISUAL OUTCOMES

Snellen BCVA at 4 weeks ranged from 20/250 to 20/30, with a median of 20/60. The mean ± SD logMAR BCVA was 0.53 ± 0.32 and the improvement from baseline was significant (P < .001).

At 8 and 12 weeks, the mean ± SD logMAR BCVAs were 0.53 ± 0.34 (median, 20/50) (P < .001) and 0.49 ± 0.32 (median, 20/50) (P < .001), respectively. Seventeen patients who were followed up for more than 12 weeks (mean, 5.3 months) had a mean ± SD logMAR BCVA of 0.45 ± 0.30 (n = 17) (P < .001) at last visit. Maximum improvement in BCVA occurred at 4 weeks after the first injection. However, further improvement was observed in subsequent follow-up as well (Figure 1).

At 12 weeks, 15 patients (47%) had BCVA of 20/40. Only 1 patient had BCVA of less than 20/200. Nineteen eyes (59%) had an improvement of BCVA of 3 lines or more, 11 eyes (34%) remained stable, and 2 eyes (6%) lost 3 or more lines (moderate visual loss) (Figure 2). The mean improvement in BCVA was 4.9 lines (range, −5 to +18 lines).
The change in BCVA of each patient from baseline to 12 weeks' follow-up is shown in a scatter diagram (Figure 3).

OCT OUTCOMES

At 4 weeks' follow-up, 15 of 32 eyes demonstrated reduction of retinal thickness and complete resolution of SRF and/or PED. At 8 weeks, an additional 12 eyes had resolution of retinal edema, SRF, and/or PED after receiving the second injection at 4 weeks. At 8 weeks, only 5 eyes had retinal edema, SRF, and/or PED, and those patients were advised to receive a third injection.

The mean±SD CMTs at 4, 8, and 12 weeks were 244.13±75.10 µm (median, 227.50 µm), 240.84±78.56 µm (median, 222.00 µm), and 236.84±62.19 µm (median, 225.00 µm), respectively. The decrease in CMT from baseline was significant at each follow-up, and the maximum reduction of CMT was observed after the first injection at 4 weeks. At 12 weeks, the mean reduction was 78.00 µm (P<.001). The change in CMT of each patient from baseline to 12 weeks' follow-up is shown in a scatter diagram (Figure 4).

The MV was measured when possible. The mean±SD baseline MV was 6.99±0.80 µL (n=22). At 4, 8, and 12 weeks, the mean±SD MVs were 6.82±0.58 µL (n=17), 6.78±0.57 µL (n=17), and 6.73±0.40 µL (n=15), respectively. Like CMT, the decrease in MV from baseline was significant at each follow-up, with a mean reduction of 0.26 µL at 12 weeks (P=.008).

REPEAT INTRAVITREAL INJECTIONS

Optical coherence tomographic findings were used to decide whether the patient should undergo retreatment. Intravitreal bevacizumab injection was repeated at a 4-week interval if OCT showed increased retinal thickness due to edema, SRF, and/or PED. A total of 55 intravitreal injections were given in this series, with a mean of 1.7 injections per eye (range, 1-4 injections/eye). Twelve patients required 2 injections, 4 patients required 3 injections, and 1 patient required 4 injections (Table). SAFETY AND COMPLICATIONS

The injection was well tolerated by all of the patients. Three patients had floaters on the day of injection. One patient developed mild iridocyclitis at day 1 after the first
A 25-year-old man developed diminution of visual acuity to 20/60 OS. Ophthalmic examination, color fundus photography, FFA, and OCT (Figure 5A, B, and C) showed subfoveal active ICNV. Intravitreal bevacizumab was injected, and at 4 weeks’ follow-up, visual acuity improved to 20/30 with marked reduction of fluid in OCT (Figure 5D). At 12 weeks’ follow-up, FFA (Figure 5E and F) showed contraction of the membrane with staining and OCT demonstrated the absence of fluid (Figure 5G).

Case 2

A 25-year-old woman had diminution of visual acuity to 20/120 OS. Ophthalmic examination, color fundus photography, and FFA showed subfoveal classic ICNV (Figure 6A and B). Optical coherence tomography revealed intraretinal edema and large multiple cystoid spaces at the fovea (Figure 6C). The patient received intravitreal bevacizumab. Although at 4 weeks there was marked reduction in CMT on OCT (Figure 6D), intravitreal bevacizumab was repeated for the residual edema. At 12 weeks’ follow-up, FFA (Figure 6E and F) showed contraction of the membrane and minimal leakage. Visual acuity was 20/60, and OCT demonstrated minimal edema (Figure 6G). The patient was asked to return for further follow-up and observation.

**SELECTED CASE REPORTS**

**Case 1**

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**COMMENT**

The natural course and outcome of ICNV is not well known and, to our knowledge, has not been studied in large series of patients. As the natural history of ICNV is better than that seen in AMD, thermal laser therapy does not appear to be a suitable treatment option because of the risk of central vision diminution immediately.5,13,16 In the Macular Photocoagulation Study for juxtapfoveal and extrafoveal CNV, 10 of 19 nontreated eyes (53%) lost 2 or more lines of vision.16 In a study by Ho et al,23 of 19 eyes (16%) had moderate vision loss during the mean observation period of 87 months.

Until now, the treatment of ICNV was aimed at destruction or selective closure of the neovascular membrane by thermal laser therapy, transpupillary thermotherapy, or PDT. Surgical management has also been tried. However, anti–vascular endothelial growth factor agents have not been evaluated in ICNV.

The introduction of PDT offered the first selective treatment for CNV, allowing for closure of CNV membranes with relative sparing of the overlying retina. Results of PDT in AMD were not satisfactory for occult or large lesions.17,18 However, in ICNV, results of PDT are reported to be more favorable.3,10

The study of transpupillary thermotherapy by Kumar et al6 showed that 11 of 21 eyes (52%) had 1 or more lines of improvement of vision, whereas 4 eyes (19%) showed a decline in BCVA in a mean follow-up of 3.1 months. As transpupillary thermotherapy has not been evaluated by others for the treatment of ICNV, its role is not well known.

Surgical removal and macular translocation in ICNV are possible, but few eyes have been treated with these modalities so far. In addition, surgery has many disadvantages, such as being invasive in nature, demanding surgical expertise, having a risk of surgical complication including retinal detachment, and possible recurrence.7,8,19,20

With the introduction of anti–vascular endothelial growth factor agents, several investigators have reported their observations following off-label treatment with bevacizumab in neovascular AMD. Avery et al12 retrospectively reviewed 81 eyes of 79 patients with subfoveal CNV secondary to AMD treated with monthly bevacizumab injections. They found that 30 of 81 eyes (37%) at 4 weeks and an additional 25 of 51 eyes (49%) at 8 weeks exhibited complete resolution of intraretinal fluid, subretinal fluid, and PED. The median visual acuity improved from 20/200 to 20/80 at 8 weeks. In our series, 15 of 32 eyes (47%) at 4 weeks and an additional 12 of 17 eyes (71%) at 8 weeks had complete resolution of fluid. At 8 weeks, the median visual acuity improved from 20/200 to 20/50. In a recent study, Bashshur et al13 reported results of intravitreal bevacizumab (2.5 mg/0.1 mL) in 17 eyes with subfoveal CNV from AMD. At 12 weeks’ follow-up, 13 of 17 eyes (76%) had complete resolution of SRF with improvement of the mean BCVA from 20/252 to 20/76. In our series at 12 weeks, 31 eyes (97%) exhibited complete resolution of SRF with a mean BCVA improvement from 20/210 to 20/47. However, Bashshur and colleagues used 3 injections of 2.5 mg/0.1 mL of intravitreal bevacizumab every 4 weeks in AMD irrespective of SRF status on OCT.

Most of the published studies on ICNV report low patient numbers with variable visual results. Currently, there are no published studies to our knowledge evaluating the efficacy or safety of intravitreal bevacizumab for subfoveal ICNV.

As bevacizumab has not been studied in a prospective, randomized, clinical trial to our knowledge,
patients should be warned about and followed up closely for potential complications. However, in our series of 32 patients, we did not find any case of retinal detachment, hemorrhage, endophthalmitis, or thromboembolic events.

In our case series of 32 eyes, all except 2 eyes had a unilateral lesion, indicating a rare prevalence of bilateral occurrence as noted in other studies. In our study at 12 weeks, 19 eyes (59%) had an improvement of BCVA of 3 or more lines, 11 eyes (34%) remained stable, and 2 eyes (6%) lost 3 or more lines. Results of PDT in ICNV vary from 25% with improvement of 1 line in a recent study to 62% with improvement of 3 lines in earlier smaller series. Fifteen eyes...
(47%) had BCVA of 20/40 or more and only 1 eye had visual acuity less than 20/200 in our series at 12 weeks' follow-up. In previous studies of ICNV treated with PDT, final BCVA of 20/40 or more was reported in 2 of 8 eyes (25%), 3 of 10 eyes (30%), 21 and 4 of 8 eyes (50%). 10 However, the duration of follow-up in our study is shorter, making it difficult to directly compare our results with those of the earlier studies.

On OCT, SRF was found to resolve faster than retinal edema, whereas PED resolved last. It was not possible to measure SRF and PED quantitatively. Only retinal edema was assessed by measuring CMT and/or MV.

Presence of SRF, PED, or cystoid macular edema is indicative of membrane activity. Without using any quantitative parameters, most of the studies have used their presence as an indication for retreatment, and this was also followed in our study. In our series, a mean of 1.7 injections per eye was administered, resulting in resolution of SRF in 31 eyes (97%) at 12 weeks. In the study by Avery et al., 12 30 of 81 eyes (37%) had complete resolution of fluid after a single injection, whereas 15 eyes (47%) in our series needed a single injection. Bashshur et al. 11 administered 3 injections of 2.5 mg/0.1 mL every 4 weeks as per their protocol in CNV from AMD and found complete resolution of SRF in 13 of 17 eyes (76%) at 12 weeks' follow-up. Although the most effective dose of intravitreal Avastin required for the treatment of CNV has not been studied, CNV may require a lesser amount of injection in comparison with neovascular AMD. However, only a comparative study can confirm this presumption.

Limitations of the BIN study are that it was a non-comparative study involving a small number of eyes, it used Snellen visual acuity measurement, and it had a short duration of follow-up. Despite these, our observations suggest that short-term use of intravitreal bevacizumab is safe and well tolerated in the management of ICNV. However, further evaluation with longer follow-up is needed to confirm long-term efficacy and safety.

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