ORIGINAL ARTICLE

MICROSTRUCTURAL EFFECTS OF INTRAVITREAL BEVACIZUMAB IN IDIOPATHIC CHOROIDAL NEOVASCULARISATION

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Background: Idiopathic choroidal neovascularization (ICNV) is a unilateral ocular disease which occurs in patients younger than 50 years and accounts for approximately 17% of patients with CNV. We evaluated microstructural effects of intravitreal bevacizumab in eyes with treatment-naïve idiopathic choroidal neovascularisation. Methods: In this case series study we reviewed the treatment and follow up records of 40 symptomatic eyes having ICNV, who received an intravitreal injection of bevacizumab (1.25 mg/0.05 mL) followed by additional doses based on optical coherence tomography findings, including intraretinal fluid, subretinal fluid, or pigment epithelial detachment. We analysed the results of best-corrected visual acuity, central retinal thickness, neovessels size (thickness and diameter), and disrupted photoreceptor length at baseline and at final visit with paired t-test. Difference in best corrected visual acuity was correlated with difference in optical coherence tomography parameters by Pearson’s correlation. Results: Mean logarithm of the minimum angle of resolution best-corrected visual acuity improved from 0.60 initially to 0.24 after treatment (p=0.01). Difference in mean central retinal thickness (82.65±44.1) µm, choroidal neovessels thickness (149.58±71.1) µm, choroidal neovessels diameter (1250.8±145.1) µm, photoreceptor disruption length (2141.20±318.8) µm were all statistically significant (p=0.01). Difference in best corrected visual acuity was correlated with optical coherence tomography parameters found no statistically significant difference. Conclusion: Intravitreal bevacizumab therapy is safe and well tolerated in ICNV eyes. Restoration of photoreceptor disruption length, decrease in central retinal thickness and choroidal neovessels size has association with visual improvement in idiopathic choroidal neovascularisation.

Keywords: Idiopathic choroidal neovascularization, Cirrus HD-OCT, Subretinal fluids, Photoreceptor disruption length, Choroidal neovascularization

INTRODUCTION

Idiopathic choroidal neovascularization (ICNV) is a unilateral ocular disease which occurs in patients younger than 50 years and diagnosed when the cause of choroidal neovascularisation (CNV) is undetermined and accounts for approximately 17% of patients with CNV.¹² Like age related macular degeneration (ARMD), compensation of CNV has been thought to be involved in the pathophysiology of ICNV but the exact mechanism is unknown.³ However, visual outcome of ICNV is favourable than CNV associated with ARMD because of its tendency for spontaneous regression.⁴ Various treatments for idiopathic CNV have been reported, such as photodynamic therapy or intravitreal anti-vascular endothelial growth factor (VEGF) therapy. However, the treatment of ICNV is still not well established.⁴ In recent years, various reports have shown that bevacizumab (Avastin; Genetech,Inc.), one of the anti-VEGF monoclonal antibodies, achieved significant visual effects in treating ICNV. Zhang et al.⁵ have followed a cohort of 40 ICNV patients for 12 months and the mean number of bevacizumab treatments were 2 injections per eye during 12 months follow-up, resulting in all lesions converting to the cicatricial stage; 40% and 70% of eyes had complete resolution of fluid after a single or an additional injection, respectively. These results suggest that idiopathic CNV required fewer injections and a single injection followed by wait-and-see approach may be more effective treatment protocol for ICNV eyes.⁶⁷

We achieved variable effects in our ICNV patients after intravitreal bevacizumab (IVB) therapy. We find it reasonable to hypothesize that visual improvement and retinal fluids resolution have correlation with microstructural changes at fovea. Therefore, we reviewed our ICNV patients OCT data and compare their parameters at baseline and final follow up. To our knowledge, this hypothesis has not been investigated in regarding the efficacy of IVB in patients with treatment-naïve ICNV according to the literature review.

MATERIAL AND METHODS

In this case series study we reviewed the records of treatment and follow up of forty eyes of 40 patients who had complaints of visual symptoms and not undergone previous treatments of intravitreal
injection of bevacizumab (1.25 mg/0.05 mL Avastin; Genentech, Inc, San Francisco, CA) for idiopathic CNV between September 2013 to December 2014. All patients were younger than 50 years and showed active CNV by ophthalmoscopy, slit-lamp biomicroscopy, fluorescein/indocyanine angiography and OCT. They have minimum follow-up of six months and had presented with active stage of CNV at baseline examination. Active stage of ICNV was defined as leakage within the macular lesion by fluorescein/indocyanine angiography and associated with intraretinal oedema or subretinal fluid, and retinal pigment epithelial detachment based on Cirrus HD-OCT. We excluded patients with CNV because of pathological myopia (refractive error ≥-6 diopter [D] or axial length ≥26 mm), clinical signs of macular degeneration, angioid streaks, presumed ocular histoplasmosis syndrome (POHS), uveitis, traumatic choroidal rupture, hereditary and macular diseases and undergone previous treatment of intravitreal anti-VEGF injection, surgery, laser photocoagulation or photodynamic therapy. Best-corrected visual acuity (BCVA), slit lamp biomicroscopy and OCT records were available for every single visit in all patients.

At baseline, all eyes had a complete ophthalmic examination, including best-corrected visual acuity (BCVA) measured by decimal visual acuity chart (converted to logarithm of the minimum angle of resolution [logMAR]), intraocular pressure, biomicroscopy, fundus photography, fluorescein or indocyanine green angiography Heidelberg Retina Angiograph 2 (HRA-2; Heidelberg Engineering, Inc., Dossenheim, Germany) and Cirrus HD-OCT (Carl Zeiss, Germany).

OCT examinations were performed with Cirrus HD OCT (Carl Zeiss, Germany) using macular cube 512×128 acquisition protocol. OCT with an 840-nm superluminescent diode and depth resolution of 5 microns, provide detail retinal images with sampling frequency of 27,000 A-scans per second.

Both eyes pupils were dilated with tropicamide 1% and phenylephrine hydrochloride 2.5% after which transverse scan of the 6x6 mm area of the macular region centered on fovea was acquired using OCT. Images were taken by a trained technician and reviewed in a masked fashion by (W.H. and C.N) and measured values for each variable were averaged for statistical analyses. Only images with signal strength greater than 6 were selected. For the purpose of this study, subretinal fluid on OCT was defined as homogeneous hyporeflective space between neurosensory retina and RPE. We defined resolution of retinal fluids as absence of subretinal fluid (SRF) evaluated on OCT scans and careful observation of FA or ICGA results through the early to late phase. The diameter of CNV was defined as the maximum horizontal margin that could be distinguished by OCT. Thickness of CNV was defined as the maximum CNV thickness above the retinal pigment epithelial level that could be determined by hyper-reflectivity. The integrity of the foveal photoreceptor layer was defined as the loss of the hyperreflective line and evaluated by using the photoreceptor IS/OS junction line on the HD-OCT images. Reduced backscattering from the IS/OS, external limiting membrane, retinal pigment epithelium was regarded to be the result of a shadowing effect rather than disruption. The above measurements were manually performed with the virtual caliper function included in the OCT (Figure 1). Central retinal thickness was measured based on the OCT software and was calculated as within a circle having 500 µm radius centered on the fovea as described in the Early Treatment Diabetic Retinopathy Study (ETDRS).

Statistical analyses were performed using SPSS for Windows (version 20.0; SPSS, Inc., Chicago, IL). The logarithm of minimal angle of resolution (logMAR) was calculated from decimal visual acuity for statistical analysis. Data were expressed as mean ± SD. Paired t-test was used to determine the significance of differences. Bivariate relationships were analysed using the Pearson correlation. For evaluation of inter observer reliability, intraclass correlation coefficient of variables (disrupted photoreceptor length, CNV size) was assessed. P values less than 0.05 were considered significant.

RESULTS
A total of 40 eyes from 40 patients were included in this study, which included 12 males and 28 females. The mean age was 30.1±7.80 years (range, 17–48 years), and the mean refractive error was −2.50±2.24 D (range, −4.50 to +0.30 D). The mean number of intravitreal injections given was 2.28±1.69 (range, 1–4), and the mean follow-up period was 3.60±1.20 months (range, 1–5 months). Among the 40 eyes, subfoveal idiopathic CNV was present in 24 eyes (60%) and juxtafoveal idiopathic CNV in 16 eyes (40%) (Table 1). The mean BCVA (logMAR) after intravitreal injection of bevacizumab improved significantly to 0.24±0.43 from a baseline BCVA (logMAR) of 0.60±0.17 (p=0.01). 32 of 40 eyes (80%) showed improvement and 8 of 40 eyes (20%) showed no change in BCVA after injection. All eyes had a final BCVA of 0.3 or better. The mean central retinal thickness at baseline was 338.67±40.2 µm which reduce to 256.03±27.80 µm (p=0.01) at final visit. Inter observer interclass correlation coefficient (ICC) for the measurements of IS/OS disrupted
length, CNV diameter and thickness were 0.71–0.85 at baseline and final follow up. These findings suggest that OCT measurements had good reproducibility in our study.

Choroidal neovessels size (thickness and diameter) at baseline was (356.55±44.8 and 1460.50±135.80) µm which reduced to (206.98±49.7 and 209.72±106.30) µm and showed statistically significant difference (p=0.01). Photoreceptors disruption length also reduce from 2337.30±40.2 µm to 256.03±27.80 µm at final visit and showed statistically significant difference (p=0.01) (Table 2). Difference in BCVA (logMAR) was correlated with OCT parameters and shows no statistically significant difference.

At final follow up after bevacizumab treatment, OCT B-scans showed absence of subretinal fluids, regression of choroidal neovessels and reduction in photoreceptors disruption length. (Figure 1). None of the patients in our study developed systemic or ocular complications after intravitreal bevacizumab, such as thromboembolic events, cerebral vascular accidents, intraocular inflammation, elevated intraocular pressure and endophthalmitis.

Image (A) obtained from a 24-year-old man with blurred vision in the right eye with subretinal fluid (SRF). Baseline visual acuity (VA) was 0.8 (logMAR), photoreceptor disruption length was 1532 µm; choroidal neovascularization (CNV) thickness and diameter were 530 µm, 384 µm respectively. Image (B) after bevacizumab intravitreal injection, subretinal fluid (SRF) was resolved, his visual acuity (VA) improved to 0.4 (logMAR). Photoreceptor layer was intact, with decrease in CNV thickness (470µm) and diameter (270µm) at final follow up.

Image (C) obtained from a 32-year-old woman with blurred vision in the right eye and subretinal fluid (SRF) associated with juxtafoveal choroidal neovascularization (CNV). Her initial visual acuity (VA) was 0.6 (logMAR), disrupted photoreceptor length was 1735 µm, choroidal neovascularization (CNV) thickness and diameter were 460µm and 579µm, respectively.

Image (D) after intravitreal bevacizumab injection, subretinal fluid (SRF) was completely resolved and visual acuity (VA) improved to 0.2 (logMAR). The inner segment and outer segment junction (IS/OS) was intact and choroidal neovascularization (CNV) size present reduction in CNV thickness (210 µm) and diameter (325 µm) at final follow up.

Figure-1: Idiopathic choroidal neovascularisation optical coherence tomography (OCT) parameters
Previous Idiopathic CNV studies have shown that decrease in central retinal thickness was related to good visual outcomes. In our study we have observed reduction in CRT at final follow up. We found that CRT decreases significantly as subretinal fluid has been absorbed after application of intravitreal bevacizumab therapy. Zhang et al.3 have followed prospectively a cohort of 40 Idiopathic CNV eyes for 2 years and reported that improvement in visual acuity was significantly correlated with decrease in CRT after intravitreal bevacizumab therapy.

The results of the present study showed that there was significant reduction in the status of the photoreceptor disruption length at the final follow up. Visual acuity was improved with the restoration of disrupted IS/OS line. The results of this study are consistent with those of previous studies in exudative ARMD, suggesting that the integrity of the photoreceptor layer is associated with visual outcome after photodynamic therapy or anti-VEGF therapy.9–11

After intravitreal anti-VEGF therapy, patients with idiopathic CNV in this study showed good visual prognosis, which is similar to findings in previous studies.5–8 Central retinal thickness, CNV size and length of disrupted photoreceptor was reduced significantly with mean number of injections per eye was 2.28 during a mean follow-up of 3.6 months. Furthermore, all lesions were in the cicatricial stage of CNV at last follow-up, with no intraretinal or subretinal fluid by OCT imaging. No ocular or systemic adverse effects occurred after intravitreal bevacizumab therapy during the follow-up period. The treatment of idiopathic CNV is still controversial, but this study coins that intravitreal bevacizumab administration for idiopathic CNV is safe and effective.

Limitations of this study need to be highlighted including its retrospective nature, absence of control group and relatively small number of patients. These limitations may have affected the evaluation of final BCVA and OCT parameters in this study.

However, we noted a clear trend toward reduction in OCT parameters in eyes with idiopathic CNV. A clear understanding of the clinical efficacy of anti-VEGF agents will require further prospective randomized-controlled clinical trials with longer follow-up, larger patient cohorts and OCT modalities with higher resolution.

CONCLUSIONS

We concluded that intravitreal bevacizumab injection improve visual acuity and reduce microstructural changes which may be involved in the pathogenesis

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**Table-1: Demographics and clinical characteristics of patients with ICNV**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age±SD, years</td>
<td>30.1±7.80 (range 17–48)</td>
</tr>
<tr>
<td>Male: Female</td>
<td>12:28</td>
</tr>
<tr>
<td>Eye (Right: Left)</td>
<td>19:21</td>
</tr>
<tr>
<td>Refractive error ±SD, D</td>
<td>2.50±2.24 (range −4.50 to +3.30)</td>
</tr>
<tr>
<td>Number of Injections</td>
<td>2.5±1.69 (range, 1–4)</td>
</tr>
<tr>
<td>Follow up period ±SD, months</td>
<td>3.60±1.20 (range, 1–5)</td>
</tr>
<tr>
<td>Location of CNV</td>
<td></td>
</tr>
<tr>
<td>Subfoveal</td>
<td>24 eyes (60%)</td>
</tr>
<tr>
<td>Juxtafoveal</td>
<td>16 eyes (40%)</td>
</tr>
</tbody>
</table>

SD; standard deviation, CNV; choroidal neovascularisation, D; diopters

**Table-2: Comparison of clinical characteristics in ICNV patients**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline ±SD</th>
<th>Final ±SD</th>
<th>Difference ±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP, mmHg</td>
<td>15.5±4.148</td>
<td>15.3±1.32</td>
<td>0.28±1.40</td>
<td>0.220</td>
</tr>
<tr>
<td>BCVA/logMAR</td>
<td>0.60±0.17</td>
<td>0.24±0.43</td>
<td>−0.36±0.24</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CRT, µm</td>
<td>338.67±40.2</td>
<td>256.03±27.80</td>
<td>82.65±44.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CNV thickness, µm</td>
<td>356.55±44.8</td>
<td>206.98±49.7</td>
<td>149.58±71.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CNV diameter, µm</td>
<td>1460.50±135.80</td>
<td>209.72±106.30</td>
<td>1250.8±145.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IS/OSS disruption length</td>
<td>2337.30±40.2</td>
<td>256.03±27.80</td>
<td>2141.20±318.8</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

p-value relate to paired t-test. IOP, Intraocular pressure; BCVA, best corrected visual acuity; CRT, central retinal thickness; CNV, choroidal neovascularisation; IS/OS, inner segment/outer segment

**DISCUSSION**

This study showed that in ICNV patients, at baseline, photoreceptors layer was disrupted, central retinal thickness was enlarged due to subretinal fluid and eruption of choroidal neovessels. To the best of our knowledge, photoreceptor disruption length and size of choroidal neovessels have not previously been reported in patients with ICNV.

Previous studies have suggested structural changes in choroidal neovessels after application of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy. Framme et al.10 observed CNV structural changes before and after anti-VEGF therapy in 78 eyes with neovascular ARMD. They reported significant reduction in CNV thickness and showed no significant difference in CNV diameter. Similarly Byun et al.11 have treated 113 neovascular ARMD eyes with intravitreal bevacizumab. They reported thicker subretinal tissues in non-responders and no significant difference in CNV diameter between groups. In our study we have significant reduction in thickness and diameter of CNV which is consistent with previous CNV reduction in thickness in exudative age-related macular degeneration (ARMD). Anatomically CNV in exudative ARMD is classified as Type 1 or Occult CNV and CNV in idiopathic CNV is classified as Type 2 or classic CNV. The authors suspect that the nature of both entities might be involved in the difference of result.
of Idiopathic CNV. Intravitreal bevacizumab is safe and well tolerated in ICNV eyes

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REFERENCES

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