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Intravitreal bevacizumab for the treatment of choroidal haemangiomas

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Key words:

anti-VEGF, bevacizumab, circumscribed choroidal haemangioma

Synopsis:

The use of intravitreal bevacizumab as an alternative to photodynamic therapy for the treatment of exudative choroidal haemangiomas was investigated. Bevacizumab treatment did not significantly improve the visual acuity, nor did it lead to the resolution of subretinal fluid. Bevacizumab is unlikely to be an effective treatment for choroidal haemangiomas.

Abstract

Purpose:

To investigate the use of intravitreal bevacizumab for the treatment of subretinal (SRF) and intraretinal fluid associated with circumscribed choroidal haemangiomas (CCH).

Methods:

This was a retrospective review of all patients treated with at least 3 bevacizumab injections for CCH-associated SRF between May 2020 and August 2023 in Moorfields eye hospital. Outcome measures included change in best corrected visual acuity (BCVA), change in patient reported symptoms, change in SRF and change in central subfield thickness (CSFT). Data on further management following cessation of injections was analysed.

Results:

The study included 9 patients. Median BCVA was 6/19 before and 6/24 after injections (p = 0.41). CSFT decreased from a median of 466 μm to 447 μm (p = 0.11). Two thirds of (n=6) patients did not show any reduction in foveal SRF, one third (n=3) showed a partial reduction and no patients had a complete resolution of SRF. Eight patients received rescue-photodynamic therapy and one received external beam radiotherapy. BCVA changed from a median of 6/60 to a median of 6/12 after rescue treatment (p = 0.63). The median CSFT decreased significantly from 470 μm to 249 μm (p = 0.01).

Conclusions:

Intravitreal bevacizumab is unlikely to be an effective treatment for exudative CCH.

Introduction

Circumscribed choroidal haemangiomas (CCH) are benign vascular hamartomas. Visual impairment can result if a CCH is associated with exudative changes in the macula, in the form of subretinal or intraretinal fluid. CCH is likely congenital, but on average patients present with symptoms in the 5th or 6th decade of life.[1] Photodynamic therapy (PDT) is currently considered the treatment of choice for visually significant exudative CCH[1, 2], double duration PDT being more effective than single duration.[2] Verteporfin (Visudyne®, Cheplapharm Arzneimittel GmbH, Greifswald, Germany) is an intravenous dye that acts as a photosensitizer during PDT. After intravenous injection, verteporfin is internalized by endothelial cells in the retinal blood vessels. Photoactivation of the verteporfin by a nonthermal diode laser results in a photochemical reaction, releasing oxygen free radicals which lead to occlusion of the targeted blood vessels in the CCH.[3]

Since May 2020 there has been an international shortage of Visudyne due to manufacturing issues.[4] Between May 2020 and March 2022 none was available in the United Kingdom and after this, supplies have been limited. This has greatly impacted on the ability to treat CCH patients. Alternative treatment options for CCH are available. These include external beam radiotherapy (EBRT), plaque radiotherapy and transpupillary thermotherapy (TTT). However, all these alternative options carry a higher risk of side effects and visual loss compared to PDT.[1]

Vascular endothelial growth factor (VEGF) is a pro-angiogenic cytokine that is known to play a role in the pathogenesis of many retinal vascular diseases. Its upregulation in certain

retinal diseases contributes to increased vascular permeability which leads to accumulation of subretinal and intraretinal fluid. Intravitreal injection of anti-VEGF agents has become a well-established, safe and effective treatment to reverse the increased vascular permeability in wet age-related macular degeneration, diabetic macular oedema and retinal vein occlusion. Several case series have reported the use of intravitreal anti-VEGF, as bevacizumab and conbercept, as a primary or secondary treatment for exudative CCH.[5-8] A study of cytokine levels in aqueous humour samples from patients with CCH has shown increased levels of VEGF.[9] Given the low risk profile of these injections, the use of intravitreal injections of bevacizumab has been proposed as an alternative to PDT given the unavailability of Visudyne. This study aims to investigate the effectiveness of intravitreal bevacizumab as an alternative treatment for exudative CCH (off-label use).

Materials and methods

The medical records of the Ocular Oncology Service at Moorfields Eye Hospital were retrospectively reviewed for patients with a diagnosis of CCH between May 2020 and August 2023. This study was registered as a clinical audit (number 1187) at Moorfields Eye Hospital and as such did not require Institutional Review Board Approval. The study adhered to the tenets of the Declaration of Helsinki.

The diagnosis of CCH was established using slit lamp biomicroscopy and multimodal imaging including ultra-widefield (UWF) fundus photography, autofluorescence imaging, optical coherence tomography (OCT), fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA) and high frequency B-scan ultrasonography (US). All patients included in the study had visual symptoms related to the presence of exudative changes in the macula

secondary to the CCH. All patients received at least 3 injections of intravitreal bevacizumab (1.25 mg / 0.05 ml), 4 weeks apart and had at least one follow-up appointment one month after the last injection. The injections were performed with an aseptic technique in a dedicated intravitreal injection suite.

Demographic data collected included patient age, sex, ethnicity and affected eye. Clinical and imaging data at baseline examination included best corrected visual acuity (BCVA), history of previous treatment for the CCH, tumour location, largest basal diameter, tumour thickness on US and tumour density on US. OCT features included presence of subretinal fluid (SRF) over the tumour and in the fovea, presence of intraretinal fluid in the fovea and central subfield thickness (CSFT). Intravitreal injection data included the number of bevacizumab injections received, the interval between injections and any injection-related complication. Data on further management of the CCH after cessation of injections was also collected.

Outcome measures included BCVA one month after the last injection, change in patient reported symptoms, change in SRF over the tumour and the fovea, change in intraretinal fluid, change in CSFT and change in tumour thickness on US.

Statistical analysis was performed using the non-parametric Wilcoxon signed-rank test for paired data using the statistical software GraphPad Prism software version 10.0.3 (Jandel software, La Jolla, USA). When p values were less than 0.05 (two tailed) the differences were regarded as statistically significant (possibility of a type I alpha error <5%).

Results

Nine patients underwent intravitreal bevacizumab treatment between May 2020 and August 2023. Patient demographics and the baseline features of the CCHs are shown in table 1. The mean age of patients undergoing treatment was 53 years (median 58, range 33 - 68). Presenting mean LogMAR visual acuity was 0.6 (Snellen 6/24) [median 0.5 (Snellen 6/18), range 0.0 – 1.5 (Snellen 6/6 – 2/60)]. Six (67%) of the patients had no treatment for the CCH prior to the intravitreal bevacizumab, while 3 (33%) patients were previously treated with PDT. The mean diameter of the CCHs was 6.8 mm as measured by UWF colour imaging and 7 mm as measured by US. The mean thickness of the CCHs on US was 1.9 mm. Eight (89%) of the CCHs were in the macula. All the CCHs showed SRF in the fovea while 4 (44%) showed intraretinal fluid in addition to the SRF.

Outcomes following treatment of the CCHs with bevacizumab are shown in table 2. Eight (89%) patients received 3 intravitreal injections of bevacizumab spaced 1 month apart, while 1 (11%) patient received a total of 6 injections. The median LogMAR BCVA was 0.5 (Snellen 6/18) [mean 0.6 (Snellen 6/24), range 0.0 – 1.5 (Snellen 6/6 – 2/60)] before injections and 0.6 (Snellen 6/24) [mean 0.6 (Snellen 6/24), range 0.0 – 1.8 (Snellen 6/6 – 1/60)] after injections ($p = 0.41$). The CSFT decreased from a median of 466 μm (mean 478 μm, range 377 – 587 μm) to 447 μm (mean 431 μm, range 316 – 536 μm) after injections ($p = 0.11$). Two thirds of (n=6) patients did not show any reduction in foveal SRF, one third (n=3) showed a partial reduction and no patients had a complete resolution of SRF. Five patients had intraretinal fluid at baseline which did not improve after bevacizumab injections. The median thickness of the CCH was 2 mm (mean 1.8 mm, range 1.0 – 2.6 mm) pre-injection, compared to 1.6 mm (mean 1.6 mm, range 0.8 – 2.7 mm) post-injections ($p = 0.72$). Seven (78%) patients reported persistent

symptoms after treatment with injections, 1 (11%) patient reported worsening of their symptoms, while 1 (11%) patient reported improvement in their symptoms (Fig 1).

The 8 patients reporting persistent or worse symptoms had further treatment of the CCH and their treatment outcomes are shown in table 3. Seven patients received rescue treatment with double duration (166s) PDT, while 1 patient received EBRT. Of the patients receiving PDT, 6 patients required a single session of double duration PDT (Fig 2), while 1 patient required 2 sessions of double duration PDT spaced 5 months apart. The median interval between the first intravitreal injection and receiving rescue treatment was 6.5 months (mean 8.6 months, range 5 – 18 months). The LogMAR BCVA changed from a median of 1.0 (Snellen 6/60) [mean 0.8 (Snellen 6/36), range 0.2 – 1.8 (Snellen 6/9 – 1/60)] to a median of 0.3 (Snellen 6/12) [mean 0.8 (Snellen 6/36), range -0.1 – 2.1(Snellen 6/5 – Counting fingers)] (p = 0.63). The median CSFT decreased significantly from 470 μm (mean 454 μm, range 314 – 617 μm) to 249 μm (mean 263 μm, range 171 – 419 μm) (p = 0.01). The median thickness of the CCHs decreased significantly from 2 mm (mean 1.9 mm, range 1.0-2.6 mm) to 0.85 mm (mean 1.0 mm, range 0.3 – 2.2 mm) (p = 0.02). Two (25%) patients reported persistent symptoms, 5 (63%) patients reported improvement in their symptoms and 1 (13%) patient reported resolution of their symptoms.

Discussion

This study investigated the use of intravitreal injections of bevacizumab in the management of exudative CCH. There was no significant improvement in visual acuity (p=0.41) nor a significant reduction of CSFT (p=0.11) after treatment with bevacizumab. Two thirds of (n=6) patients did not show any reduction in foveal SRF, one third (n=3) showed a partial

reduction and no patients had a complete resolution of SRF. Most patients (n=7, 78%) required rescue treatment with PDT when Visudyne could eventually be obtained. Despite a significant reduction of CSFT (p=0.01) and complete resolution of foveal SRF in all patients after rescue PDT treatment, the visual acuity did not improve significantly (p = 0.63).

Several case reports and small series have suggested the beneficial effect of anti-VEGF in the treatment of exudative CCH. Sagong et al, reported on 3 cases of CCH treated with intravitreal bevacizumab. One case received a single injection of bevacizumab and showed resolution of SRF and visual improvement 1 month after the injection with no signs of recurrence during 8 months of follow up. The other 2 cases received a single injection of bevacizumab as a pre-treatment before PDT. Both cases showed an improvement in SRF 1 week after the injection, before the administration of PDT.[8] Mandal et al, similarly reported on 3 cases. Two patients received two injections of bevacizumab 6 weeks apart, after non-response to TTT in one case and laser photocoagulation in the other. Both showed improvement in BCVA, serous detachment and CMO, which was maintained over 12 months of follow up. The third patient received one injection of bevacizumab as a primary treatment for a CCH. OCT showed improvement in serous detachment after 6 weeks. The patient received a further injection in combination with laser photocoagulation. No further improvement was noted and the initial response was maintained over 12 months.[7]

Subsequent studies have demonstrated that not all cases of CCH are responsive to anti-VEGF injections. A case report described a patient with an exudative CCH who showed no anatomical or visual improvement after two intravitreal injections of ranibizumab. The patient was subsequently treated with one session of PDT. The SRF resolved and the vision improved from 20/50 to 20/25.[10] Kwon et al, reported on 9 cases receiving intravitreal bevacizumab. Four

patients received bevacizumab as a primary treatment for CCH, while 5 patients received it as a secondary treatment for recurrent or persistent SRF following TTT. Overall, 56% of the patients showed resolution of the SRF, while 44% had persistent SRF. There was a significant reduction of the median central foveal thickness (CFT) from 514 µm to 251 µm. The median LogMAR visual acuity improved significantly from 0.7 to 0.5 after injections. Of the 4 patients receiving bevacizumab as a primary treatment, 2 showed resolution of the SRF while 2 showed persistent SRF. Of the 5 patients receiving bevacizumab as a secondary treatment, 2 showed resolution of the SRF, 1 showed persistent SRF and 2 showed worsening of the SRF. Intraretinal fluid was present in 4 out of these 5 patients. All 4 patients showed persistent intraretinal fluid, despite 2 of them showing resolution of the SRF.[5] Lai at al, prospectively investigated the effectiveness of intravitreal conbercept injections as a primary treatment for exudative CCH.[6] Conbercept is an anti-VEGF recombinant fusion protein developed in China and approved by the Chinese Food and Drug Administration in 2013. It combines domains of the VEGF-receptor-1 and VEGF-receptor-2 to the Fc portion of human IgG-1.[11] Lai et al, treated 42 patients, 55% of which were sensitive to conbercept showing resolution of the SRF. The mean number of injections was 3.83 in 6 months. The remaining 45% required rescue PDT or laser photocoagulation as they were non-responsive after 3 injections of conbercept. At 3 months, the mean LogMAR visual acuity showed a non-significant improvement from 0.92 to 0.82, while the mean CFT decreased significantly from 534 µm to 400 µm for the whole group. Similar results were observed for the subgroup of patients responsive to conbercept. The mean LogMAR visual acuity showed a non-significant improvement from 0.84 to 0.76 and the mean CFT decreased significantly from 427 µm to 259 µm at the 6 months final follow up. The same pattern was observed for the patients requiring rescue PDT. The mean LogMAR visual acuity showed a non-significant improvement

from 1.08 to 0.71 and the mean CFT decreased significantly from 725 µm to 418 µm at 6 months.[6]

The response to anti-VEGF injections was poor in our case series compared to most of the aforementioned studies. None of our patients showed resolution of SRF. The ethnic background of the patients included in these studies was different from ours. Kwon et al. and Lai et al. were treating patients of an East Asian background, while most of our patients were of a white Caucasian background. Lai et al. studied the effect of conbercept rather than bevacizumab, thus the results are not directly comparable. Bevacizumab is a humanized monoclonal antibody that binds all isoforms of VEGF-A. Conbercept is an anti-VEGF recombinant fusion protein. It acts as a decoy receptor that binds to all isoforms if VEGF-A, VEGF-B, VEGF-C and placental growth factor with higher affinity than bevacizumab.[11]

The thickness of the CCHs was not influenced by intravitreal bevacizumab injections, but showed a significant reduction after rescue PDT. This is consistent with previous reports.[1, 6] The lack of a significant visual improvement after rescue PDT despite a good anatomical improvement might be related to the delay in availability of Visudyne. The delay between administering intravitreal bevacizumab and administering rescue PDT in our patients ranged from 5 to 18 months. The chronicity of the exudative changes in the macula could have led to permanent damage of photoreceptors.

The current study has some limitations, specifically the small number of cases and its retrospective nature. In conclusion, contrary to previous studies, it appears that intravitreal bevacizumab is not an effective treatment option for exudative changes associated with a CCH. Based on the results of this study, enthusiasm for intravitreal bevacizumab as an alternative to

PDT should be tempered, in favour of the latter for this indication. Larger studies are needed to verify these results and to explore the effectiveness of different anti-VEGF drugs.

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Figure legends

Figure 1

Male patient, 33 years old, presented with an exudative circumscribed choroidal haemangioma (CCH). Best corrected visual acuity (BCVA) was 6/6 and he reported distortion in vision. (A) Widefield fundus image showing the CCH in the inferotemporal part of the macula. (B) Early phase indocyanine green angiography (ICGA) image showing hypercyanescene of the CCH. (C) Late phase ICGA image showing partial washout of the dye from the CCH. (D) Optical coherence tomography (OCT) scan of the fovea at presentation showing subretinal fluid (SRF) and intraretinal fluid (IRF). (E) OCT scan 1 month after 3 intravitreal injections of bevacizumab showing persistent SRF and IRF. BCVA remained 6/6. (F) OCT scan after photodynamic therapy showing resolution of SRF and IRF. BCVA improved to 6/5 and the patient's symptoms resolved.

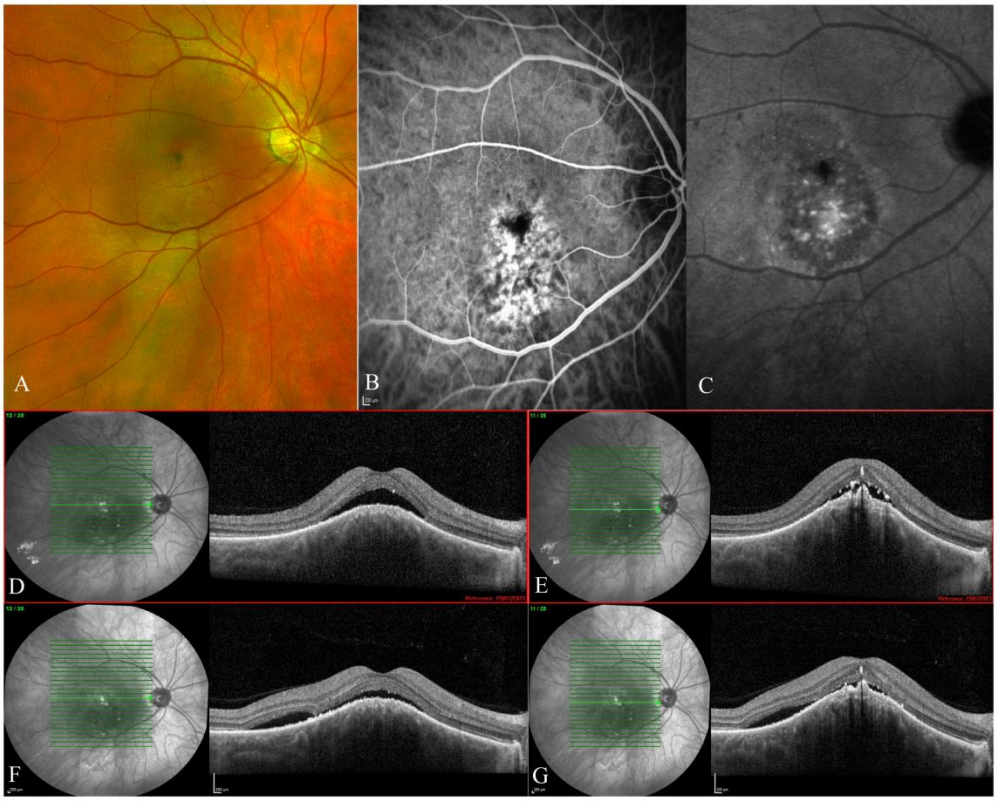

Figure 2

Male patient, 41 years old, presented with an exudative circumscribed choroidal haemangioma (CCH). Best corrected visual acuity (BCVA) was 6/9 and he reported distortion in vision. (A) Widefield fundus image showing the CCH under the fovea. (B) Early phase indocyanine green angiography (ICGA) image showing hypercyanescene of the CCH. (C) Late phase ICGA image showing partial washout of the dye from the CCH. (D) and (E) Optical coherence tomography (OCT) scans of the fovea at presentation showing subretinal fluid (SRF) and hyperreflective subretinal deposits. (F) and (G) OCT scans 1 month after 3 intravitreal injections of bevacizumab showing reduced height of subretinal fluid (SRF) in the fovea and appearance of new SRF over the edge of the CCH. BCVA remained at 6/9 and the patient reported partial improvement in his symptoms. The patient decided not to have any further treatment.

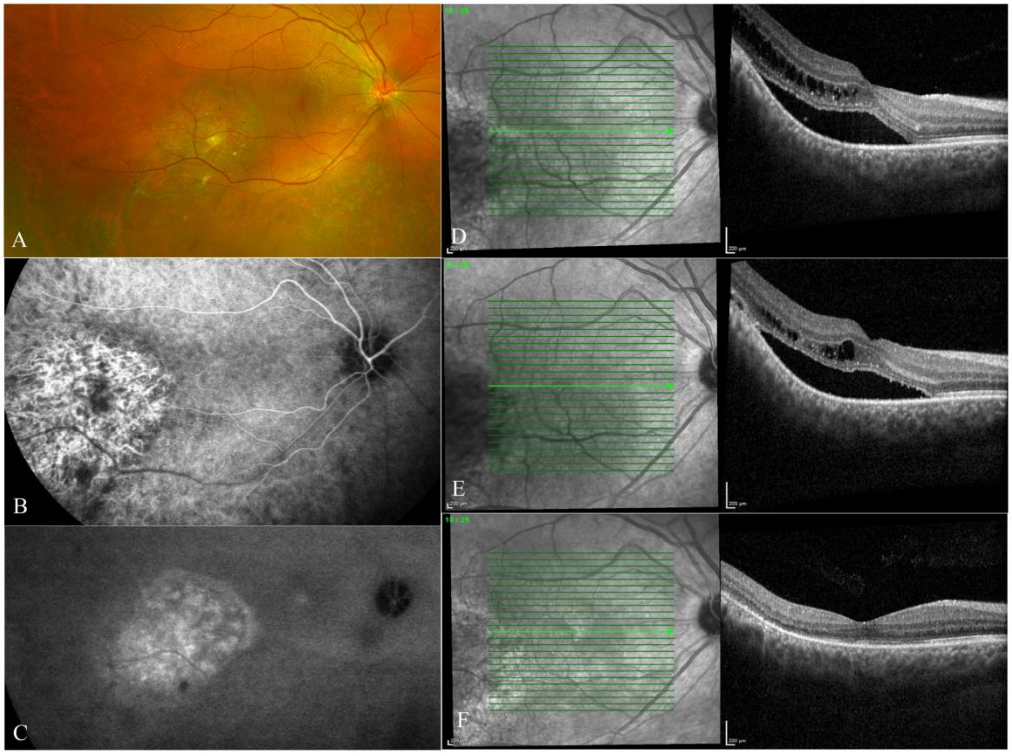

Table 1. Intravitreal bevacizumab for the treatment of choroidal haemangiomas: Patient demographics and baseline features.

Demographics	**Number (%), n=9**
Age (years) mean (median, [range])	53 (58, [33-68])
Sex	
Male	7 (78)
Female	2 (22)
Race	
White	4 (44)
Other	3 (33)
Not recorded	2 (22)
Eye	
Right	7 (78)
Left	2 (22%)
Baseline visual acuity	
Snellen mean (median, [range])	6/24 (6/18, [6/6 – 2/60])
LogMAR	0.6 (0.5, [0.0

mean (median, [range])	– 1.5])
Previous treatment of the choroidal haemangioma	
None	6 (67%)
Photodynamic therapy	3 (33%)
Clinical and imaging features of choroidal haemangioma:	
Diameter (ultra-widefield colour imaging), mm mean, (median, [range])	6.8 (7.0, [3.6-11.0])
Diameter (ultrasound), mm mean, (median, [range])	7.0 (7.4, [3.9-10.9])
Thickness (ultrasound), mm mean, (median, [range])	1.9 (2.0, [1.0-2.6])
Distance to foveola (from tumour edge), mm mean, (median, [range])	-0.7 (-1.3, [-3.5 - 2.2])
Distance to optic disc (from tumour edge), mm mean, (median, [range])	1.8 (0.9, [0-4.3])
Epicenter quadrant	
Macula	8 (89)
Superior	1 (11)

Temporal	0 (0)
Inferior	0 (0)
Nasal	0 (0)
Epicenter anteroposterior location	
Macula	8 (89)
Macula to Equator	1 (11)
Equator to Ora Serrata	0 (0)
Internal reflectivity on ultrasonography	
High	2 (22)
Medium	6 (67)
Low	1 (11)
Lipofuscin on autofluorescence	
Yes	6 (67)
No	3 (33)
Fluid location on optical coherence tomography	
Subretinal	9 (100)
Intraretinal and subretinal	4 (44)

Table 2. Intravitreal bevacizumab for the treatment of choroidal haemangiomas: Outcomes

Treatment outcomes of intravitreal bevacizumab	**Number (%), n=9**
Follow up (months) mean (median, [range])	15 (16, [8 – 23])
Number of injections	
3	8 (89)
6	1 (11)
Visual acuity (LogMAR)	
Pre-injections mean, (median, [range])	0.6 (0.5, [0.0 – 1.5])
Post-injections mean, (median, [range])	0.6 (0.6, [0.0 – 1.8])
Wilcoxon Signed-Rank Test	p = 0.41
OCT findings:	
Central subfield thickness, μm	
Pre-injections mean, (median, [range])	478 (466, [377 – 587])
Post-injections mean, (median, [range])	431 (447, [316 – 536])

Wilcoxon Signed-Rank Test	p = 0.11
Subretinal fluid in the fovea	
No change	6 (67)
Improved but not resolved	3 (33)
Subretinal fluid over the haemangioma	
No change	7 (78)
Worse	2 (22)
Cystoid macular oedema	
None present pre-injections	4 (45)
No change	3 (33)
Worse	2 (22)
Ultrasound thickness, mm	
Pre-injections mean, (median, [range])	1.8 (2.0, [1.0 – 2.6])
Post-injections mean, (median, [range])	1.6 (1.6, [0.8 – 2.7])
Wilcoxon Signed-Rank Test	p = 0.72
Patient reported symptoms	
Persistent	7 (78)
Worse	1 (11)
Improved but not resolved	1 (11)

OCT: optical coherence tomography, PDT: photodynamic therapy.

Table 3. Intravitreal bevacizumab for the treatment of choroidal haemangiomas: Post-injection management of choroidal haemangiomas.

Post-injection management of choroidal haemangioma	**Number (%), n=8**
Post-injection treatment modality	
PDT (1 session, double duration)	6 (75)
PDT (2 sessions, double duration)	1 (12.5)
EBRT	1 (12.5)
Visual acuity (LogMAR)	
Pre-further treatment mean, (median, [range])	0.8 (1.0, [0.2 – 1.8])
Post-further treatment mean, (median, [range])	0.8 (0.3, [-0.1 – 2.1])
Wilcoxon Signed-Rank Test	p = 0.63
OCT findings:	
Central subfield thickness, μm	
Pre-further treatment mean, (median, [range])	454 (470, [314 – 617])
Post-further treatment	263 (249, [171 –

mean, (median, [range])	419])
Wilcoxon Signed-Rank Test	p = 0.01*
Subretinal fluid in the fovea	
Resolved	8 (100)
Subretinal fluid over the haemangioma	
Resolved	8 (100)
Cystoid macular oedema	
None present pre-injections	3 (37.5)
Improved but not resolved	2 (25)
Resolved	3 (37.5)
Thickness of choroidal haemangioma, mm	
Baseline (US) mean, (median, [range])	1.9 (2.0, [1.0-2.6])
Post-further treatment (US or EDI-OCT) mean, (median, [range])	1.0 (0.85, [0.3 – 2.2])
Wilcoxon Signed-Rank Test	p = 0.02*
Patient reported symptoms	
Persistent	2 (25)
Improved but not resolved	5 (62.5)
Resolved	1 (12.5)

PDT: photodynamic therapy, EBRT: external beam radiotherapy, OCT: optical coherence tomography, US: ultrasound, EDI: enhanced depth imaging

*The result is significant at $p < 0.05$.