Intra-vitreal bevacizumab in patients with Juvenile Vitelliform Dystrophy (Best Disease)

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Juvenile Vitelliform Dystrophy (Best disease) is a degenerative macular condition that is genetically inherited. In recent years monoclonal antibodies have been employed to help prevent the decline in vision associated with macular fluid. This report documents the use of intra-vitreal bevacizumab in two siblings (aged thirteen and fifteen) with Best Disease. This work studies the changes observed in visual acuity and macular oedema over a 39 and nineteen week period respectively.

Introduction

Juvenile Vitelliform Dystrophy (Best disease) is a rare genetic condition which damages the posterior pole of the eye over many years. It is caused by an abnormal *VMD2* gene located on the long arm of chromosome 11 [1] (11q12-q13) with inheritance via autosomal dominance. [2] A confident estimate of the incidence of this condition has not been made; however, due to its genetic nature, cases tend to appear in clusters. The largest sample of this sort has been found in Sweden, where 250 cases of Best disease were traced to a single (presumably homozygous) carrier who lived in the 17th century. [3] Afflicted individuals are initially asymptomatic, with a normal fovea and the only abnormality detectable present on electro-oculography (EOG). [4] The stages of Best disease are summarised in Table 1. Changes in visual acuity first occur usually between the ages of three and fifteen and coincide with the development of classic macular lesions of an egg-yolk ('vitelliform') appearance. Vision may remain stable from this point until a patient reaches their 40s, when acuity may decrease markedly. [5] Relatively recent developments in the use of monoclonal antibodies to reduce macular oedema may offer treatment benefits in this rare condition. In 2007, Leu *et al*. [6] reported functional and morphological improvement over six months in a patient of similar age treated for choroidal neovascularisation with intra-vitreal bevacizumab on the background of Best disease. However, other reports of patients being treated in this fashion are scarce.

Table 1. *Stages of Best Disease.*

Stage	Description
0 (Normal)	Normal visual acuity fundoscopic appearance. Abnormal EOG.
1 (Pre-vitelliform)	Pigment mottling of the macula. Visual acuity remains largely unaffected.
2 (Vitelliform)	Appears in early childhood. Features a round "egg-yolk" macular lesion. Visual acuity is mildly reduced (between 6/6 and 6/15).
3 (Pseudo-hypopyon)	Usually occurs during puberty. Part of the lesion is absorbed with minimal effect on visual acuity.
4 (Vitelliruptive)	Lesion atrophies and visual acuity reduces (to as low as 6/60).

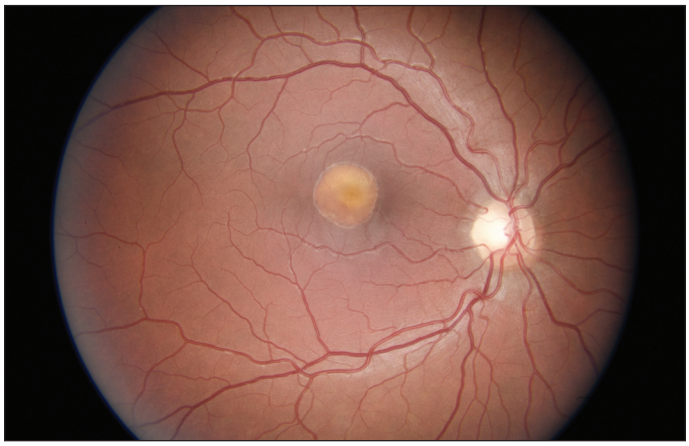

Figure 1. *Right fundus of Case One, eighteen months prior to the time of presentation with decreased left visual acuity. A vitelliform macular lesion typical of Best disease is present.*

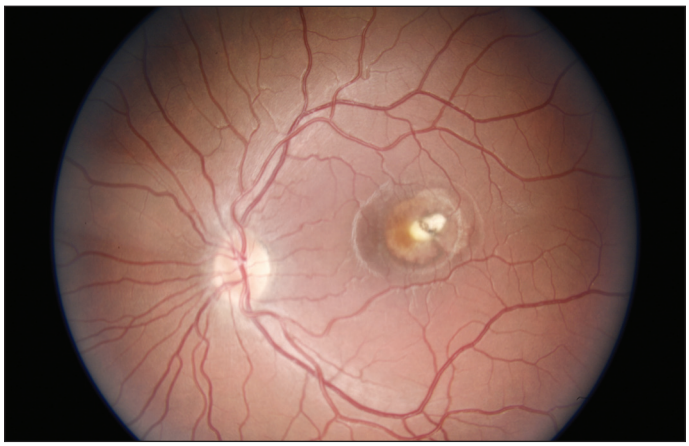

Figure 2. *Left fundus of Case One, eighteen months prior to time of presentation with decreased left visual acuity. A vitelliform macular lesion typical of Best disease is present.*

This work attempts to contribute additional information about the short term effects of bevacizumab when used for Best disease.

The Cases

The following report documents the effect of intra-vitreal bevacizumab on visual acuity and macular oedema in two siblings (aged thirteen and fifteen) with Best disease. Their father also has the condition and is legally blind. Informed consent to publish a report of the cases was obtained from the patients and their mother.

Case One

A thirteen year old male previously known to suffer from Best disease, stage two (Figures 1 and 2), presented eighteen months later with decreased left visual acuity. Fundus examination showed

classical bilateral vitelliform lesions as well signs of a left sub-retinal haemorrhage (Figures 3 and 4). This diagnosis was confirmed with fluorescein angiography (Figure 5) which also indicated the leakage of fluid within the vitelliform lesion.

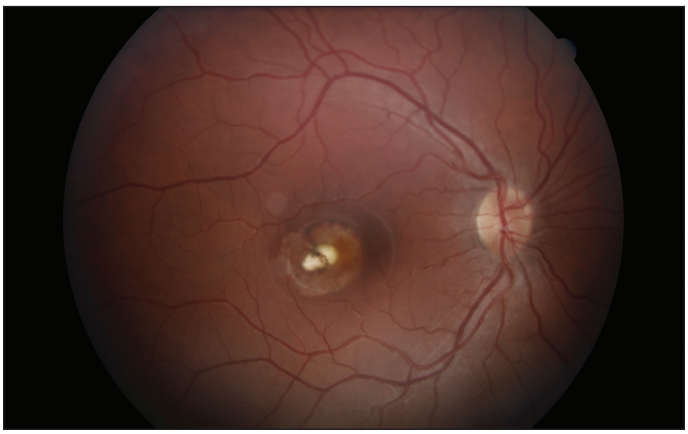

Figure 3. *Right fundus of Case One at the time of presentation with a vitelliform macular lesion.*

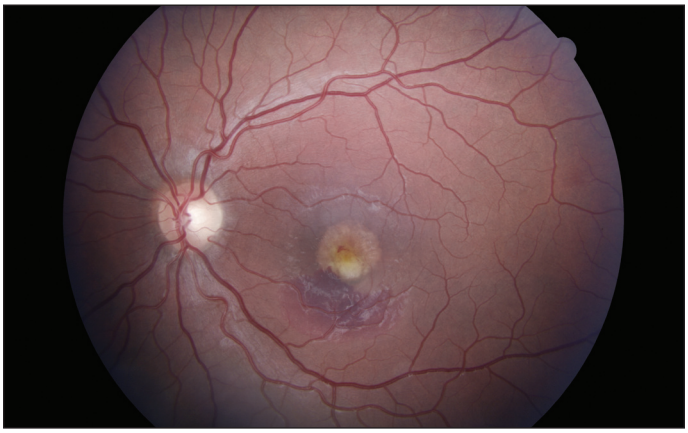

Figure 4. *Left fundus of Case One showing a classical vitelliform macular lesion with subretinal haemorrhage. Intra-vitreal bevacizumab was administered to the eye later on the same day.*

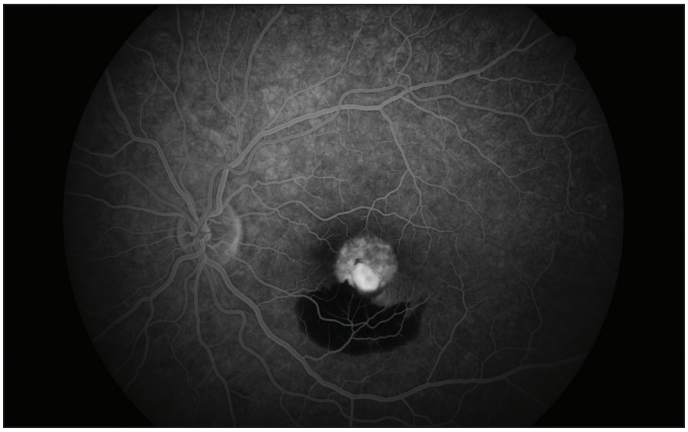

Figure 5. *Fluorescein angiography of the left fundus of Case One shows the presence of a sub-retinal haemorrhage (black region inferior to the fovea). Fluorescein dye is viewable in the overlying retinal blood vessels; however fluorescence is obscured from the choroid. By contrast, pooling of dye is evident within the vitelliform lesion.*

Comparison between examination findings at the time of presentation with fundus photos acquired eighteen months previously suggested the vitelliform lesions had become further advanced. Treatment of the left sub-retinal haemorrhage consisted of two doses of intra-vitreal bevacizumab (3mg/0.12ml per dose) administered to the left eye four weeks apart. The patient was observed through examination of visual acuity and spectral domain optical coherence tomography (SOCT Copernicus, Optopol S.A., Zawiercie, Poland). Eight weeks following the first bevacizumab treatment an improvement in visual acuity was observed. Furthermore, reduced macular oedema associated with the vitelliform lesion was also identified (Figures 6 and 7). In light of these improvements, intravitreal bevacizumab was subsequently administered to the right eye. Over a 39 week period of observation, visual acuity improved bilaterally (Table 2) despite the return of some macula oedema in the left eye (Figure 8).

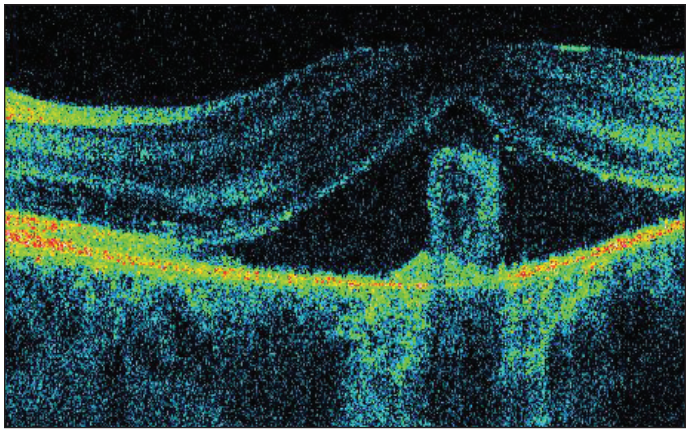

Figure 6. *OCT of the left fovea of Case One prior to administration of intra-vitreal bevacizumab shows the presence of macular oedema.*

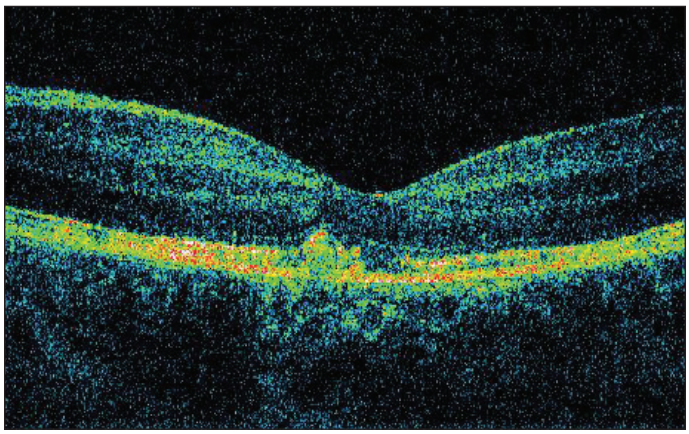

Figure 7. *OCT of left fovea eight weeks following initial bevacizumab treatment (Case One). Macula oedema is much reduced.*

Table 2. *Changes in visual acuity over 39 weeks in a thirteen year old male undergoing treatment for Best disease with intra-vitreal bevacizumab. At follow-up 39 weeks after the commencement of treatment, visual acuity has improved in both eyes.*

Weeks from date of first bevacizumab treatment	BCVA (right dye)	Right bevacizumab	BCVA (left eye)	Left bevacizumab
0	6/12+		6/9pt	#1
3	6/12all		6/12all	
4	6/12-		6/15-	#2
8	6/12-		6/7.5pt	
11	6/12pt		6/9.5+	
12	6/12+	#1	6/6pt	
16	6/9.5pt		6/6pt	
20	6/15pt		6/6pt	
23	6/9pt	#2	6/6-	
27	6/9pt		6/6-	
31	6/9.5pt		6/6all	
39	6/9.5pt		6/4.8-	

Legend: All BCVA (best-corrected visual acuity) measurements were recorded from Snellen and Bailey-Lovie visual acuity charts.

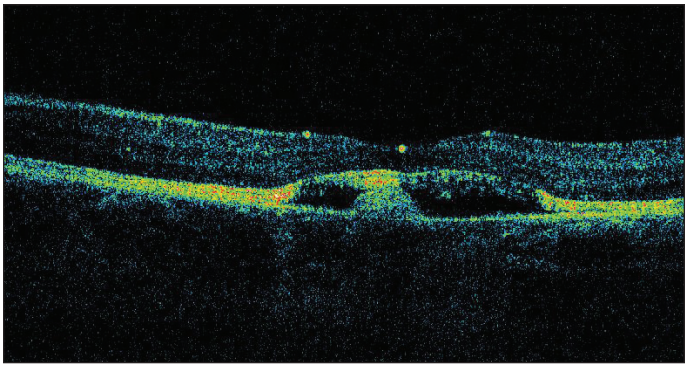

Figure 8. *OCT of left fovea 39 weeks following initial bevacizumab treatment (Case One). Some oedema is present, despite improved visual acuity. The lucent area under the neurosensory retina is due to the vitelliform lesion itself and may not indicate persisting choroidal neovascularisation.*

Cross-sectional view of the right macular on optical coherence tomography (OCT) remained relatively unchanged throughout the period of observation, despite a small improvement in right visual acuity (Figures 9 and 10). Further information regarding this case and initial follow-up of the intervention has been previously included in a scientific poster. [7]

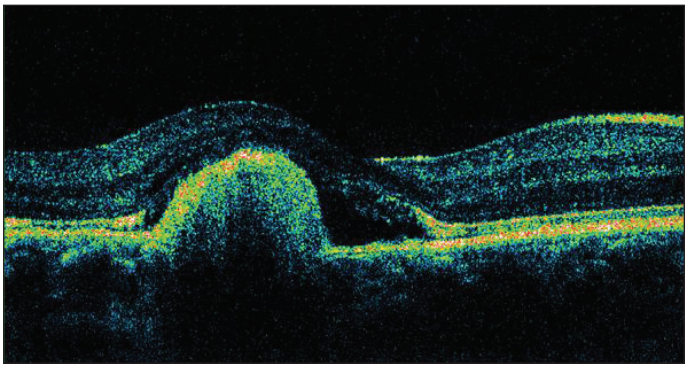

Figure 9. *OCT of right fovea of Case One prior to administration of intra-vitreal bevacizumab. There is evidence of macular oedema, as well a subretinal area of lucence likely to be due to the vitelliform lesion.*

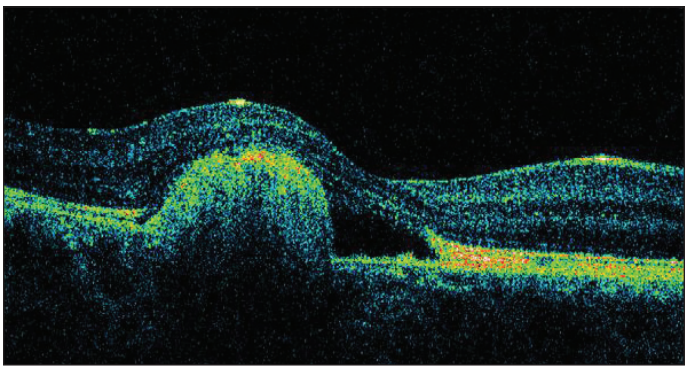

Figure 10. *OCT of right fovea of Case One, 27 weeks after initial administration of intra-vitreal bevacizumab. Compared with OCT acquired before treatment (Figure 9), a change in the level of oedema is not evident, despite a modest improvement in right visual acuity.*

Comparison with previous fundus photography (Figure 1) indicated that this lesion had progressed. Intra-vitreal bevacizumab was injected into this eye twelve weeks following the acquisition of this image.

Case Two

A fifteen year old female with Best disease (stage two) presented for review. Examination with OCT revealed the presence of bilateral macular oedema (Figures 11 and 12). Intra-vitreal bevacizumab was used in both eyes, initially in the right eye and three weeks subsequently in the left. Whilst minimal change was observed in the level of macular oedema four months after the initial injections (Figures 13 and 14) visual acuity showed a mild improvement (Table 3).

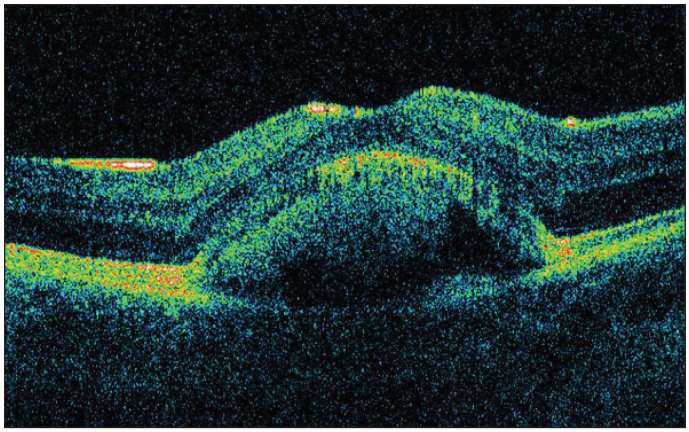

Figure 11. *OCT of right fovea of Case Two prior to administration of intra-vitreal bevacizumab. Macular oedema is evident, as is subretinal translucence suggesting the presence of a vitelliform lesion.*

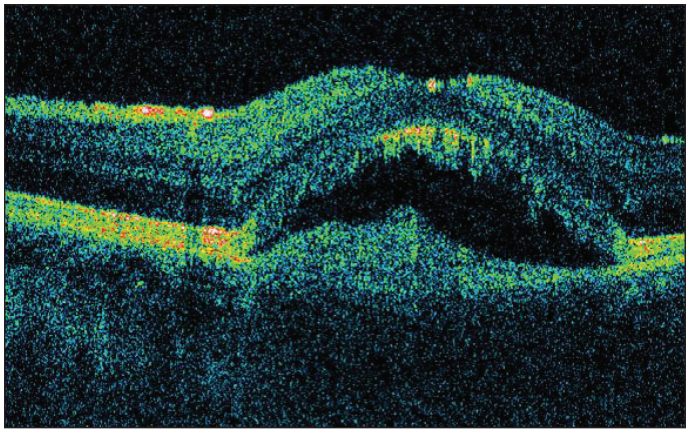

Figure 12. *OCT of left fovea of Case Two prior to administration of intra-vitreal bevacizumab. Macular oedema is evident, as is subretinal translucence suggesting the presence of a vitelliform lesion.*

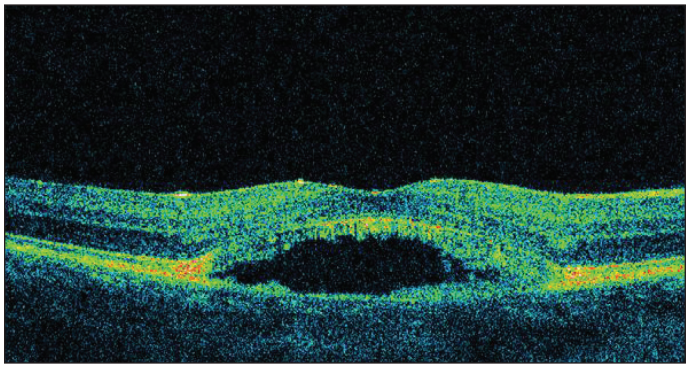

Figure 13. *OCT of right fovea of Case Two examined nineteen weeks after initial administration of intra-vitreal bevacizumab. Macular oedema remains present, despite an improvement in visual acuity.*

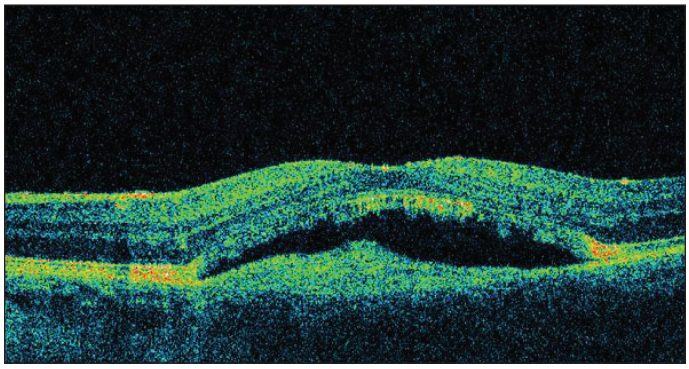

Figure 14. *OCT of right fovea of Case Two examined sixteen weeks after initial administration of intra-vitreal bevacizumab. Macular oedema remains present, despite an improvement in visual acuity.*

Table 3. *Changes in visual acuity over ninteen weeks in a fifteen year old female undergoing treatment for Best disease with intra-vitreal bevacizumab. Nineteen weeks after since the commencement of treatment, visual acuity has improved in both eyes.*

Weeks from date of first bevacizumab treatment	BCVA (right dye)	Right bevacizumab	BCVA (left eye)	Left bevacizumab
0	6/7.5all	#1	6/7.5all	
3	6/6pt		6/7.5+	#1
7	6/7.5all		6/7.5-	
11	6/6all		6/7.5-	
19	6/4.8-	#2	6/4.8pt	#2

Legend: All BCVA (best-corrected visual acuity) measurements were recorded from Snellen and Bailey-Lovie visual acuity charts.

Discussion

German Ophthalmologist, Franz Best, first described this hereditary condition in multiple members of a family in 1905. [8] Almost a century later, the identification of abnormalities of the *VMD2* gene (also referred to as *BEST1*) as the clear cause of the condition has provided clues as to why macular degeneration takes place in this patient group. It is known *VMD2* encodes for the trans-membrane protein bestrophin, which functions as a calcium-ion-dependant chloride channel within the retinal pigment epithelium. [9,10] Furthermore, additional work has shown that abnormal bestrophin protein forms malfunctioning calcium-ion-dependant chloride channels. [11] At present, the exact mechanism by which these abnormal channels produce the macular degeneration in Best disease is not fully understood. Existing hypotheses suggest that retinal pigment epithelial cells degenerate as a result of any one or more of abnormal cell volume, altered extra-cellular fluid composition or damage to cellular organelles from a changed ionic environment. [12]

Treatment of neovascular ('wet') macular degeneration with monoclonal antibodies such as bevacizumab (and also ranibizumab) has come about after the identification of vascular endothelial growth factor (VEGF) as a modulator of choroidal neovascularisation. [13,14] These monoclonal antibodies inhibit VEGF, thereby limiting the resultant oedema associated with poor quality neovascular capillaries. [15] To date, VEGF has not been identified as a contributing factor to the macular degeneration observed in Best disease. However, the altered cellular conditions resulting from abnormal calcium-ion-dependant chloride channels may indirectly provoke the localised release of VEGF. Determining the presence of high levels of VEGF in patients with Best disease would greatly further the case for management with monoclonal antibodies. However the answer to this question falls far beyond the bounds of this paper. Best lesions are not usually associated with choroidal neovascularisation. However these cases appear to have developed these complications. The relationship between these patients as siblings may have genetic significance.

A noteworthy topic is the use of OCT to monitor for macular changes during the treatment period. Previously, fluorescein angiography has been the primary investigation tool for monitoring the progression of macular oedema. [16, 17] However, OCT has been successfully used by previous workers [18,19] to observe the cross-sectional anatomy of affected eyes. Practical advantages of OCT use in these cases include the speed of image acquisition and lack of need for intravenous fluorescein. Whilst seemingly insignificant, these factors are noteworthy when repeated examinations are required in young patients.

The visual outcomes of the cases observed in this report suggest a temporary benefit of intra-vitreal bevacizumab in Best disease. In all four eyes of the two siblings treated, visual acuity showed at least mild improvement after four and nine months of follow-up respectively. Furthermore, a reduction in macular oedema was observed. That only two cases have been observed is a clear limitation to any conclusion. However, due to the extremely low incidence of Best disease, it is unlikely that trials of this therapy in this group of patients will ever be possible. Short term vision improvement is of particular benefit to young patients, such as the two cases in this report. Both patients are currently attending secondary school, where visual acuity needs are high.

From this work, it is impossible to determine whether long term benefits to visual acuity of patients with vitelliform macular lesions exist. Best disease has a poor visual prognosis, so a positive long term finding for any therapy would be welcomed with open arms by patients and clinicians alike. The critical issue to be addressed by future workers in this area pertains to whether increased levels of VEGF are present in the eyes of patients with Best disease. If found to be an effective treatment, determining the long term effects of intra-vitreal bevacizumab in this condition will require a concerted effort from the medical community, including longer term follow-up of visual acuity in larger numbers of patients.

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Conflict of interest

None declared.

Consent Declaration

Informed consent to publish a report of the cases (and relevant figures) was obtained from the patients and their mother.

Copyright

Information in this case report has not been previously published elsewhere, nor is it under submission for review with any other publishing organisation.

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