Clinical outcomes of treated macular neovascularisation secondary to inherited retinal diseases: a literature review

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ABSTRACT

Many inherited retinal diseases (IRD) can be associated with, or be secondarily complicated by, macular neovascularisation (MNV), which has been variably treated with intravitreal antivascular endothelial growth factor, steroids, laser and surgery. In this article, we aim to present a consolidated literature review of management of IRD-related MNV.

INTRODUCTION

The pathogenic mechanisms involved in various inherited retinal diseases (IRDs) result in progressive damage to photoreceptors, retinal pigment epithelium (RPE), Bruch’s membrane (BM) and choriocapillaris, which rarely could promote secondary macular neovascularisation (MNV), leading to severe and acute loss of vision on the background of pre-existing visual deficits. Without treatment, the majority of these lesions progress to form a fibrotic scar with variable visual outcomes. Various treatment modalities have been used in the management of MNV secondary to IRDs as evidenced from published case series and isolated case reports. In this narrative literature review, we discuss treatment of MNV associated with IRDs and related clinical outcomes.

BACKGROUND

Although it is well known that IRDs can be associated with secondary MNV, there are no accurate data on the prevalence of MNV in different IRDs, while it is understood that macular dystrophies carry a higher risk. Commonly, MNV in IRDs is of type 2 (ie, classic choroidal neovascularisation (CNV)) and involves proliferation of fibrovascular tissue from the choriocapillaris into the subretinal space through defects in BM and the RPE. The more common occurrence of neovascularisation in the macula compared with peripheral retinal involvement, has been postulated to be due to differences in the lamina elastica of BM, which is thinner and more porous in the macula and additionally suffers more degenerative changes with age than the peripheral BM. Given that IRDs are a large group of heterogenous conditions driven by specific genetic variants that affect retinal structure and function in different ways, the pathogenesis of MNV in IRDs is likely to be influenced by the causative genetic variant in many instances. However, mechanisms postulated to result in disruption of the RPE-BM complex that then promote MNV, include reduced choroidal blood flow, reduced choroidal perfusion, impaired RPE transport function, increased intravascular pressure resulting in RPE detachments, imbalance between proangiogenic and anti-angiogenic factors and abnormal extracellular matrices of BM, RPE and vascular endothelial cells. Chronic inflammation has also been postulated as a mechanism for MNV in IRDs.

METHODS

We conducted a PubMed search in January 2022 with no date restrictions for articles published in English language using the following keywords and Boolean operators: (choroidal neovascularisation OR macular neovascularisation) AND (inherited OR hereditary OR dystrophy) and additionally searches for individual conditions—adult onset foveomacular vitelliform dystrophy, autosomal recessive bestrophinopathy, Best dystrophy, Bietti crystalline dystrophy, choroideremia, autosomal dominant drusen OR Doyne honeycomb retinal dystrophy, enhanced S-cone syndrome, gyrate atrophy, North Carolina macular dystrophy, Oliver McFarlane syndrome, pattern macular dystrophy, retina pigmentosa, Sorsby fundus dystrophy, Stargardt disease, fundus flavimaculatus. We updated our literature review in September 2022. If the title and abstract were relevant, an article was reviewed in full.
Articles not describing active therapeutic intervention were excluded after due review.

RESULTS
The management of MNV/CNV secondary to IRDs is discussed under the heading of different diseases. The terms MNV and CNV have both been used interchangeably to denote neovascularisation in the macula. Genotyping results have not been consistently available in published cases but have been included where available (online supplemental table).

Autosomal recessive bestrophinopathy
Madhusudhan et al and Hussain et al have described cases of CNV treated with three 4-weekly intravitreal ranibizumab and bevacizumab, respectively. They both reported improvement in VA with no recurrence of CNV during the follow-up period of 1–2 years. However, the case presented by Madhusudhan et al had persistent cystoid macular oedema (CMO), which is a hallmark of autosomal recessive bestrophinopathy (ARB) that fluctuated during the follow-up period. Iannaccone et al also showed success with serial intravitreal bevacizumab over 2 years with most of the improvement in VA occurring after three injections. Moreira et al described an 8-year-old female who successfully underwent bilateral vitrectomies and surgical excision of the CNV (prior to photodynamic therapy (PDT)/anti-vascular endothelial growth factor (VEGF) availability) with improvement in VA. Ten years later, the optical coherence tomography (OCT) scans showed macular schisis in both eyes for which she had four intravitreal anti-VEGF injections and a 6-month course of dorzolamide eye-drops without success. Therefore, she underwent sequential vitrectomies with removal of the internal limiting membrane and C3F8 gas in both eyes that improved her VA. There was mild recurrence of the intraretinal cystic spaces 2–3 months postsurgery, however, these remained stable with stable VA at 1 year.

Best dystrophy
MNV in Best dystrophy, diagnosed on OCT angiography (OCTA), has been reported to have a high prevalence of up to 35%. MNV has been variably described as being both exudative and non-exudative in different stages of Best dystrophy and can occur in earlier stages such as vitelliform and pseudohypopyon stages, and not necessarily as a late complication. PDT has been shown to be successful in the treatment of CNV in numerous case reports. These patients have had 1–3 applications of PDT with no recurrences of CNV over a follow-up period ranging from 2 to 8.75 years. Interestingly, some cases have shown delayed improvement in VA over time, although with scarring. Nobrega et al reported a case where PDT alone was unsuccessful initially, however, VA improved with combined PDT and intravitreal triamcinolone and, remained stable with no recurrence at 14 months. Argon laser photocoagulation has also been reported to be successful in one case with no recurrences over 1 year.

Moreover, a single intravitreal injection of ranibizumab has improved VA with resolution of CNV and no recurrences over a follow-up period of 4 months to 3 years. Batioglu et al also showed similar results when treated with three 4-weekly injections of intravitreal ranibizumab. Another study described a patient with type 2 CNV who had clinical features and genetically proven Best disease, however, with a normal electro-oculogram. There was minimal improvement in VA with two 4-weekly intravitreal ranibizumab injections and no active CNV (clinically) at 3 years. This patient already had developed subfoveal fibrosis pretreatment. Subbiah et al reported the outcomes of children aged 5–8 years who were treated with intravitreal ranibizumab. They reported resolution of CNV with no recurrences in two patients treated with 0.5 mg of intravitreal ranibizumab followed up to 1 and 3 years. However, there were recurrences of the CNV at 1 year in two other patients treated with 0.25 mg of intravitreal ranibizumab. One of these cases had transient anterior chamber inflammation that was successfully treated with a 1-week course of topical steroids. Good visual and anatomical outcomes at 1 month was also described using a combined approach with a single intravitreal injection of ranibizumab and PDT. Recurrence at 8 months was treated with a single intravitreal injection of ranibizumab and vision with a fairly stable VA at 4 years (0.2 at 1 month and 0.3 at 4 years).

There are multiple reports that demonstrated successful treatment with 1–4 injections of intravitreal bevacizumab with improved VA, resolution of CNV and no recurrences from 0.5 to 8 years after the last treatment. However, poor functional and anatomical response to two 4-weekly intravitreal bevacizumab was reported in one study, with persistence of the CNV. Khan et al presented the functional outcomes of 14 eyes of 12 patients (11 Best dystrophy and 1 ARB) with a median follow-up period of 2.8 years (0.8–6 years). Seven eyes were treated with intravitreal bevacizumab (1.25 mg/0.05 mL; single injection in 4 cases and, 2, 3 and 10 injections in 1 case each) and 7 eyes were observed. The median gain in VA was greater in the treated versus observed group (0.46 vs 0.17 decimalised units of Snellen, p<0.05). Cakir et al presented a 11-year-old female who was treated with combined intravitreal bevacizumab (1.25 mg) and triamcinolone acetonide. The authors reported an improvement in VA at 1 month and shrinkage of CNV at 2 months post treatment with no recurrence at 6 months on fluorescein angiography (FA). The hypothesis was that triamcinolone potentiated the anti-angiogenic effect of bevacizumab reducing the need for repeated injections, decreases vascular permeability and reduces inflammation.

Bietti crystalline dystrophy
Hua et al treated a patient with a single intravitreal bevacizumab which lead to regression of CNV at 1 month but
recurred at 3 months. However, other authors have described cases where patients were treated with three 4-weekly bevacizumab and ranibizumab with subsequent improvement in VA and no recurrences over a follow-up period that ranged from 4 to 12 months.

Choroideremia

MNV is rarely reported in choroideremia, in affected males and in female carriers. Spontaneous resolution is known, and MNV may go undiagnosed as visual symptoms and signs of exudation are minimal. Treatment with intravitreal bevacizumab and ranibizumab have shown to either maintain or improve VA.

Doyne honeycomb retinal dystrophy (Malattia Leventinese and EFEMP1 retinal dystrophy or autosomal dominant drusen)

This condition is characterised by extensive drusen and can be complicated by MNV in advanced stages, which has been successfully treated with intravitreal bevacizumab, except one case where the VA continued to reduce despite an anatomical improvement.

Enhanced S-cone syndrome

MNV has been reported in 14 of 93 (15.1%) patients with enhanced S-cone syndrome in a group of patients from Saudi Arabia, all of whom subsequently developed subretinal fibrosis. Of the 10 patients who had genetic testing, all of them had mutations in the NR2E3 gene. Three patients were treated with intravitreal bevacizumab, all of whom developed fibrotic lesions at the macula with no improvement to vision. In contrast, other studies have shown improvements in VA with intravitreal bevacizumab and ranibizumab, latter with no recurrence at 7 years. Type 3 MNV showing retinochoroidal anastomoses has been described in three eyes of two patients with enhanced S-cone syndrome; one eye was successfully treated with a course of intravitreal bevacizumab.

Gyrate atrophy

There are isolated case reports of treatment with bevacizumab and ranibizumab in MNV associated with gyrate atrophy where both the MNV and VA stabilised promptly with a single injection and a course of three 4-weekly injections, respectively.

North Carolina macular dystrophy

Bakall et al successfully treated a patient with reduced vision and retinal fluid on OCT, although no convincing evidence of a CNV on FA with intravitreal bevacizumab. Other studies reported using intravitreal ranibizumab and bevacizumab, although details of the outcome of injections were not clear in the literature.

Oliver McFarlane syndrome

Although more than 30 cases of Oliver McFarlane syndrome have been published, only 1 case that was complicated by CNV has been reported in a 10-year-old female who was treated with a single intravitreal bevacizumab injection and then a single intravitreal ranibizumab injection for recurrence 2 years later. In this case, VA continued to be stable 6 years after the initial diagnosis.

Pattern macular dystrophy

Pattern macular dystrophy (PMD) represents a rare group of disorders with generally a favourable prognosis, unless complicated by MNV which in one case series was suspected in 50% of patients. Parodi et al described a prospective series of 13 eyes with MNV associated with reticular pattern dystrophy, treated with PDT with more than 50% of their patients losing more than 15 letters at 3 years, concluding that alternative therapies need to be explored.

Parodi et al prospectively assessed patients with PMD (10 with reticular dystrophy and 2 patients with adult-onset foveomacular vitelliform dystrophy (AOFVD)) associated with subfoveal CNV who were treated with three 4-weekly intravitreal bevacizumab 1.25 mg and then on a pro re nata (prn) basis. The mean VA was 0.73±0.34 logMAR at baseline and 0.43±0.23 logMAR at 24 months, with only one patient losing one line compared with baseline vision. Moreover, nine patients only required the loading doses to reach stabilisation of CNV that was confirmed on FA and OCT. Other three patients required up to eight further injections in the follow-up period.

PMD has also been successfully treated with intravitreal ranibizumab. One of these cases was initially treated with three 4-weekly intravitreal bevacizumab injections and then laser photocoagulation before being given a single intravitreal ranibizumab injection. The VA improved from 20/50 to 20/30 at 1 month and 20/20 at 8 months after the injection with regression of the CNV. However, she required two more injections of ranibizumab due to reduction in VA to 20/40 over the next 6 months and VA improved to 20/25. Lee et al described two patients in the same family with PMD simulating fundus flavimaculatus (FFM) with secondary CNV who had C213W mutation in the PRPH2 gene who were with intravitreal anti-VEGF injections (bevacizumab, ranibizumab and aflibercept) on a prn basis. Minnoun et al treated 20 patients (24 eyes) with occult CNV secondary to AOFVD with 3 4-weekly intravitreal ranibizumab and then on a prn basis as per predetermined criteria over 12 months. Mean number of intravitreal ranibizumab given was 4.5±1.29 at final visit. The VA improved (≥3 lines) in 25% of patients, did not change in 62.5% and worsened (≥3 lines) in 12.5% of patients. Of the three patients who had worsened VA, one developed macular atrophy and the other two patients had persistence of a serous retinal detachment without evidence of active CNV. Overall, the mean VA did not change significantly over the follow-up period (0.37±0.2 logMAR vs 0.30±0.25 logMAR, p=0.115). Similarly, another study showed the mean VA to improve from 0.36±0.1 at baseline to 0.56±0.1 (p=0.038) with improvement of the metamorphopsia in six female patients with occult CNV as diagnosed on FA who were treated with three 4-weekly intravitreal ranibizumab injections.
Retinitis pigmentosa

The prevalence of MNV in retinitis pigmentosa (RP) is variable among studies, with an Italian retrospective study looking at 176 eyes with RP reporting MNV prevalence to be 1.7%. Cheng et al reported successful treatment of CNV with PDT in two patients with improvement in VA and no recurrence during the follow-up period of up to 2 years. CNV has also been treated successfully with intravitreal bevacizumab and ranibizumab, with stable or improved VA and resolution of CNV although with fibrosis in some cases. However, VA failed to improve in one case (56-year-old female) despite being treated with 34 intravitreal injections over 6 years (bevacizumab, pegaptanib, ranibizumab and aflibercept).

Sorsby fundus dystrophy

Studies have shown argon laser photocoagulation and PDT for CNV secondary to Sorsby fundus dystrophy to be ineffective, necessitating anti-VEGF therapy. However, one case reported successful treatment of an extraretinal classic CNV treated with PDT at months 0, 3, 6 and 12 (due to fresh leakage on FA) with a small subretinal scar and improved VA from 6/36 to 6/12 (maintained for 1 year). CNV has been managed successfully with both intravitreal bevacizumab and ranibizumab, although majority of the studies reported recurrences requiring multiple injections. Tsokolakis et al suggested that a treat and extend protocol was more effective compared with a pro re nata protocol in reducing recurrence of CNV. Prager et al presented a case where the patient was managed with three 2-weekly intravenous bevacizumab injections (patient refused PDT and intravitreal treatments). VA improved with one episode of recurrence requiring one additional treatment at 7 months. There were no serious ocular or systemic side effects. A systematic review by Baston et al reviewed 31 cases that were treated with intravitreal anti-VEGF injections with a mean follow-up of 54 months. Treatment was given between 0 and 9 months following the onset of CNV, with an average of 5.4 months (not reported in 8 cases). They concluded that better functional outcomes are observed when treated immediately after the onset of CNV compared with delayed treatment.

Combined treatment with PDT and intravitreal triamcinolone has also shown promising results. Kapoor et al treated their patient with a single intravitreal bevacizumab injection initially, however, this patient required multiple injections thereafter for recurrences and developed bevacizumab-related intraocular inflammation after the eighth injection. The patient was subsequently treated with a combination of PDT, intravitreal dexamethasone (200 μg in 0.05 mL) and intravitreal bevacizumab, the latter two medications being continued long term. At 7 years, VA (20/50) was worse than at initial presentation (20/30), with normal intraocular pressure, cataract and, macular scarring and atrophy. Atan et al successfully managed their patient with multiple courses of oral and sub-Tenon’s injections of steroids for recurrent CNV that was initially presumed to be secondary to punctate inner choroidopathy, however, later confirmed as Sorsby fundus dystrophy on genetic analysis.

Stargardt disease and fundus FFM

FFM is a late-onset phenotypically similar condition to Stargardt disease (SD) CNV associated with SD has required repeated PDT for either persistent leakage or recurrences on FA. Querques et al reported a patient with SD and CNV who was successfully treated with three consecutive monthly intravitreal injections of ranibizumab and no recurrence at 6 months. Battaglia Parodi et al presented a prospective case series involving three patients who were treated with ranibizumab injections on a prn regimen and followed up for 24 months (4-weekly clinical examination with OCT and 3-monthly FA). A mean of 11 (9–14) injections were required over the 24 months, with only one patient showing reactivation at the end of this period. Mean VA improved from 0.47±0.06 logMAR at baseline to 0.90±0.17 at 24 months. Over the follow-up period, the area of RPE atrophy enlarged in all three cases with development of outer retinal tubulations, which is may be explained by the natural history of this condition.

Two cases of MNV in FFM were treated successfully with a single application of PDT and showed no signs of recurrence over 9–21 months. However, 2–3 applications of PDT were required in two other published cases, due to persistent leakage on FA, with improved VA. CNV secondary to FFM was also managed successfully with a single intravitreal ranibizumab injection in one patient who had no recurrence at 10 months and, in another patient who required a second injection for recurrence at 3 months and remained stable at 9 months. Quijano et al managed their patient with FFM with a course of three 4-weekly injections of ranibizumab and showed improved VA, resolution of the CNV with scarring at 6 months after the last treatment. Roy et al presented a patient with CNV and choroiditis on a background of FFM. The patient had a full uveitic workup that did not show any positive associations. There was an improvement in VA, resolution of the inflammation and the CNV with a tapering course of oral steroids and three 4-weekly intravitreal bevacizumab injections. The authors stated that the inflammatory component may have been a random association or indeed suggests a role of inflammatory pathways in Stargardt-like diseases. In another case of FFM, three 3-monthly intravitreal injections of aflibercept in combination with PDT showed resolution of CNV with scarring, but no significant improvement in the VA.

DISCUSSION

Efficacy of anti-VEGF and photodynamic therapy in IRD-related MNV

MNV in the above discussed IRDs seems to respond favourably to anti-VEGF therapy in most instances,
although there is no consensus that can be drawn with regard to an effective treatment regime. Currently, of the intravitreal anti-VEGF drugs ranibizumab is licensed to treat IRD-related MNV, however, bevacizumab and rarely aflibercept have also been used in reported cases, with comparable results. PDT has been successfully used either in isolation or in combination with intravitreal anti-VEGF or steroid therapy in RP, Stargardt and Best disease, however, visual outcomes with PDT in eyes with Sorsby dystrophy have been disappointing in most reported cases and these patients may require more continuous periods of anti-VEGF therapy, given the tenacity of associated MNV.54 72 73

In assessing treatment response based on macular OCT scans, it is important to remember that many IRDs are affected by CMO, macular schisis, outer retinal tubulations and degenerative cysts intraretinally and subretinal hyporeflective spaces due to resorbed vitelliform material, which might confound exudative changes related to MNV. Signs of exudation from MNV may also be minimal. Caution needs to be exercised in interpreting OCT scans for CNV presence and persistent activity and the use of adjunctive retinal imaging and a thorough clinical examination will prove vital. Also, even in instances where the CNV is successfully treated, visual prognosis is limited by the degree of severity of the underlying IRD and patient expectations need to be duly managed.

Safety of anti-VEGF and photodynamic therapy in IRD-related MNV

Safety of anti-VEGF in the context of IRDs has been questioned, in particular in RP and SD. In vitro and in vivo studies have shown increased oxidative stress in retinal ganglion cells97 and apoptosis of inner and outer nuclear layers of the retina98 with VEGF neutralisation. These studies suggest a neuroprotective effect of VEGF. Moreover, degeneration of the choriocapillaris, RPE and BM, thereby causing photoreceptor dysfunction was observed in mice lacking soluble forms of VEGF99 and on neutralisation of VEGF.100 However, other authors have shown that anti-VEGF treatment has not been associated with progression of visual field defects and therefore disease progression, in RP, over long follow-up periods.65 69 In contrast, another study in the context of SD suggested that the retinal atrophic changes noted during the follow-up period may have been accelerated by VEGF inhibition.60

While anti-VEGF therapy has been safely used to treat MNV in children with IRD, it is important to be aware of relative contraindications from systemic associations in patients with syndromic IRD and pregnancy. In older patients, macular dystrophies mimicking age-related macular degeneration need to be considered before planning intervention; myopic CNV may occur independent of the disease pathology of the underlying IRD as high myopia is often concomitant with many IRDs.

In certain IRDs, it has been speculated that excessive ingestion of mutant proteins by the RPE cells engaged in phagocytosis might have compromised their viability and that the mechanism of action of PDT may add further insult leading to their apoptosis and poor visual outcomes.57 Due to the rarity of cases treated with conventional argon laser or steroids, no comparisons with anti-VEGF therapy can be made with regard to outcomes; however, with the former, there have certainly been more concerns over making RPE atrophy worse, resulting in undesirable visual consequences.57

CONCLUSIONS

Secondary MNV is a rare complication of IRDs as is evident from the paucity of published cases. As described in this review, there is no consensus on the management of MNV secondary to IRD. Given that therapeutic intervention confers better visual outcomes than observation, it is prudent to offer anti-VEGF therapy and approach treatment with a personalised management plan. Judicious use of all available multimodal retinal imaging tools in diagnosing and managing IRD-related MNV is advisable. Newer non-invasive imaging modalities such as OCTA may prove helpful in understanding treatment response better.60 77 Better elucidation of genotype-phenotype correlations in IRDs, better understanding of disease mechanisms driven by the effect of particular pathogenic variants on proteins involved in retinal health and function might help to understand which patients are at increased risk of MNV development and would need active monitoring for early detection and treatment.

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REFERENCES


Sohn EH. Responsiveness of choroidal neovascular membranes in patients with R345W mutation in fibulin 3 (Doyne honeycomb retinal dystrophy) to anti-vascular endothelial growth factor therapy, Arch Ophthalmol 2011;129:1826.


