Eye (2010) 24, 203–213

www.nature.com/eye

REVIEW

Intravitreal bevacizumab for choroidal neovascularisation secondary to causes other than age-related macular degeneration

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Abstract

Choroidal neovascularisation (CNV) is characterised by new blood vessel growth under the retina that usually results in significant visual impairment when the fovea is involved. Though CNV is more commonly associated with age-related macular degeneration (AMD), it can occur secondary to a variety of other diseases. Recent successes with anti-angiogenic therapies suggest that they may outperform other therapies for all types of CNV. As non-AMD-related CNV cases are rare, randomised controlled trials are often not possible. This review compares the less prevalent reports of non-AMD CNV and pools evidence on the success and limitations of a variety of therapies.
Eye (2010) **24,** 203–213; doi:10.1038/eye.2009.201; published online 7 August 2009

Keywords: bevacizumab; non-AMD; choroidal neovascularisation

Background

Choroidal neovascularisation (CNV) can cause visual loss because of exudation of intraretinal or subretinal fluid, haemorrhage, or fibrosis at the macula.[1] Age-related macular degeneration (AMD) and pathologic myopia are the most common causes of CNV. Less common causes include angioid streaks, inflammatory conditions such as punctate inner choroidopathy, multifocal choroiditis, ocular histoplasmosis syndrome, and hereditary retinal diseases.[2] A diagnosis of idiopathic CNV (INCV) is made when no apparent cause of CNV can be determined. Non-AMD-related CNV has a younger age of onset than AMD CNV and typically presents as a smaller type 2 lesions, with CNV growing above the RPE and with a 'classic' appearance on angiography.[3]

Vascular endothelial growth factor (VEGF) is an important pro-angiogenic factor that is normally produced by RPE and retinal photoreceptors. In CNV, the RPE initiates and supports abnormal neovascularisation.[3,4] A recent development in the treatment of CNV is the use of pharmacologic agents that block VEGF. Several recent reports have shown that intravitreal injection of anti-VEGF agents such as pegaptanib sodium (Macugen), ranibizumab (Lucentis), and bevacizumab (Avastin) are effective in the treatment of both AMD and non-AMD CNV. Pegaptanib (Macugen, Eyetech Pharmaceuticals, New York, New York, USA) is an aptamer that targets VEGF 165,[5] and ranibizumab (Lucentis, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA) is an antibody fragment that targets all VEGF isoforms.[6,7] Bevacizumab (Avastin, Genentech, South San Francisco, California, USA) is an anti-VEGF drug originally developed to treat metastatic carcinoma of the colon and rectum and is a recombinant humanised monoclonal antibody against all VEGF isoforms.[8,9] Although this drug is 'unlicensed' for intraocular use, it has been widely used as intravitreal therapy for all types of CNV. In fact, reports about bevacizumab treatment of CNV far outnumber those about other anti-VEGF agents for CNV treatment.

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Received: 28 March 2009
Accepted in revised form: 6 July 2009
Published online: 7 August 2009

As non-AMD-related CNV cases are rare, it is not often possible to rely on randomised controlled trials for evidence on how best to manage these cases. The objective of this review is to compile and analyse the current evidence on the use of intravitreal bevacizumab to treat CNV in non-AMD patients.

Methodology

We conducted a systematic search of MEDLINE for publications between January 2004 and May 2009. The National Institutes of Health clinical trial databases were also searched for ongoing trials in these areas up to May 2009. For the database searches, we used the following terms or term combinations: CNV, anti-VEGF, bevacizumab, avastin, AMD, age-related maculopathy, retinal degeneration, retinal inflammation, uveitis, choroiditis, retinal dystrophy, myopia, angioid streaks, punctate inner choroidopathy, choroidal rupture, trauma, and idiopathic. Our search strategy combined keywords and medical subject heading terms. We included all data that could be extracted from the abstracts of articles in languages other than English. Visual acuity values were converted to log minimum angle of resolution (logMAR) units where appropriate. We included all reports on subfoveal non-AMD CNV that had described treatment with bevacizumab, with a minimum of 3 months follow-up. There were two main criteria for excluding reports; we excluded reports that did not provide visual or anatomical outcomes, those that involved extrafoveal CNV, or those that involved systemic bevacizumab.

We extracted two main outcome measures from all collected reports. The first is the mean change in best-corrected visual acuity at designated time points. The second is the mean number of treatments required for each condition at specified time points. In addition, we noted all reported complication rates in all reports. We also compared the visual outcomes achieved with bevacizuamb treatment to other published treatments for each condition.

Pathological myopia

High myopia affects approximately 2% of the global population. Ethnic origin seems to influence the likelihood of developing pathologic myopia, as prevalence is high in Asian populations, and low in African and Pacific island groups.[10] Myopic maculopathy is the main cause of vision loss among highly myopic patients and is the leading aetiology of subfoveal CNV among patients younger than 50 years. Nearly 10% of eyes with degenerative retinal findings consistent with high myopia develop CNV.[11] The precise pathogenesis of myopic CNV remains unclear. However, some authors have suggested that mechanical tissue strain caused by stretching may lead to the development of choroidal ischaemia, followed by atrophy of both the RPE and the overlying retina, and the subsequent release of growth factors.[12]

The visual prognosis of untreated myopic CNV is generally poor because of the associated progressive retinal atrophy. The natural history data on myopic CNV indicate that visual outcomes may be variable for up to 3 years. For most patients, obvious decline is noted after this variable period, and approximately 95% of patients decline to a visual acuity of $\geqslant$20/200 by 10 years.[13]

Therapeutic options

There are several treatments for myopic CNV, but they show limited efficacy. These include thermal laser photocoagulation,[14] photodynamic therapy (PDT),[15] macular translocation,[16] and surgical removal of CNV tissue.[17] The frequency of CNV complications undermines these treatments and generally bears poor long-term results.

Photodynamic therapy Evidence for the use of PDT for subfoveal myopic CNV is based on a Verteporfin PDT study (VIP).[18,19] In this prospective, multicentre, randomised controlled trial, a statistically significant positive visual outcome was noted at 12 months. Specifically, 72% of PDT-treated eyes lose fewer than eight letters, whereas only 44% of placebo-treated eyes show this outcome. However, this effect was not sustained at 2 years, likely because of expansion of macular atrophy caused by the treatment. The mean number of treatments required in the first year was 3.4, and 5.1 treatments were performed over the 2-year period.[18,19] A combination of intravitreal triamcinolone and PDT have also been attempted to reduce treatment rates and improve visual outcomes.[20] However, these data are limited.

Anti-VEGF agents There are more reports about intravitreal bevacizumab treatment than treatment with the other two anti-VEGF agents, ranibizumab and pegatanib sodium. There are two published reports on ranibizumab and one for pegaptanib sodium treatment.[21–23] Treatment outcomes after intravitreal bevacizumab in 15 studies are summarised in Table 1.[24–38]

A cumulative analysis of all study data reveals the following trends. Of all studies examined, a total of 181 eyes received treatment for naïve lesions, and 74 eyes were treated earlier. Of the earlier treatments, 72 included PDT and 2 included sub-tenon's triamcinolone. The dosing schedule varied between studies. A majority of eyes ($n=174$) were treated with one injection,

Table 1 Published studies on the use of intravitreal bevacizumab in myopic CNV

Type of study	*Author*	*Dose of bevacizumab (mg)*	*Treatment regimen*	*No.[a] of eyes*	*Mean refractive error*	*Mean age (years)*	*BCVA (logMAR)[b]*		*Previous treatment*	*Total follow-up (months)*	*Mean no. of treatments*
							Baseline	*Final*			
Prospective case series	Chan *et al*[25]	1.25	0, 1, 2 m: repeat same cycle if leakage at 3 months	22	−10.30	45.6	0.6	0.35	11 patients had PDT[c]; mean 3 PDT sessions	6	1.09
Retrospective case series	Yamamoto *et al*[38]	1.25	stat + prn[d]	11	NA	55.2	0.84	0.48	5 patients had PDT	6	1.27
Retrospective case series	Sakaguchi *et al*[34]	1	stat + prn	8	−15.50	50	0.58	0.28	2 patients had sub-tenon's triamcinolone	4.8	1.37
Prospective case series	Ruiz-Moreno *et al*[33]	1.25	0, 1, 2 cycle, then prn	26	−14.00	49.5	0.56	0.32	11 patients had PDT; mean 2.5 PDT sessions	6	1 cycle
Prospective case series	Hernandez-Rojas *et al*[27]	2.5	stat + prn	14	−13.87	53.86	0.95	0.56	None	3	1.28
Retrospective case series	Mandal *et al*[30]	1.25	stat + prn	12	−11.25	46.5	1.05	0.55	None	7.08	1.58
Retrospective case series	Silva *et al*[35]	1.25	stat + prn	26	−3.90	53.3	0.7	0.4	11 eyes had PDT	6	2.50
Prospective case series	Arias *et al*[24]	1.25	stat + prn	17	−12.00	55.4	0.86	0.68	9 patients had PDT	6	1.10
Retrospective series	Rensch *et al*[31]	1.5	0, 6, 12 weeks	13	NA	56.3	0.63	0.52	None	6.2	1 cycle
Case report	Tewari *et al*[36]	1.25	stat + prn	1	−14.00	21	1.00	0.10	PDT	6	2
Retrospective case series	Laud *et al*[29]	1.25	stat + prn	4	−14.00	49.75	0.39	0.29	4 eyes had PDT	6	2.20
Prospective case series	Wu *et al*[37]	2.5	stat + prn	8	−9.80	41.5	0.62	0.1	None	14.9	1.4
Retrospective case series	Rheaume and Sebag[32]	2.5	stat + prn	10	−10.6	64.4	0.62	0.34	3 eyes had PDT; mean 1.67 PDT sessions	9.7	2.6
Prospective case series	Gharbiya *et al*[26]	1.25	0, 1, 2 + prn	20	−9.80	53	1.2	0.86	2 patients had PDT	12	4
Retrospective case series	Ikuno *et al*[28]	1	stat + prn	63	−11.40	58.4	0.57	0.33	None	12	2.4

[a]No., number.
[b]BCVA, best-corrected visual acuity.
[c]PDT, photodynamic therapy.
[d]prn, pro re nata, for this and all subsequent tables.

Table 2 Analysis of visual outcomes after bevacizumab treatments of myopic CNV

	Bevacizumab dose (mg)			
	1.0 mg (n = *71*)	*1.25 mg* (n = *140*)	*1.5 mg* (n = *13*)	*2.5 mg* (n = *31*)
Baseline	0.58	0.84	0.63	0.70
Final visual acuity at 6 months	0.27	0.47 l	0.52	0.29
Mean number of injections	1.71 (1.37–2.40)	1.36 (1.1–1.58)	1 cycle	2.25

followed by additional injections *pro re nata* (*prn*). A total of 81 eyes were treated with an initial cycle of monthly injections for 3 months, followed by an optical coherence tomography (OCT)-guided re-treatment.

Pooled study data analysis We pooled and analysed common variables among the bevacizumab studies. Overall, the dose of bevacizumab varied from 1 to 2.5 mg. The mean number of injections was 1.65 (range: 1.1–2.20) at 6 months and 2.49 (range: 1.4–3.6) at 12 months. Eyes that received a cycle of monthly injections for first 3 months required an average of one cycle. At 6 months, the change in visual acuity for naïve patients (baseline 0.81 logMAR to 0.48 logMAR) was better than earlier treated patients (0.68 logMAR to 0.40 logMAR). However, at 12 months, there was no significant difference in visual acuity between these patient groups (Table 2).

Different end points were used in most studies. However, on average, 64–68% eyes gained 15 or more letters at the end of 6 months and this gain was maintained in 40–44% eyes at the end of 12 months in studies that reported 12 months outcomes.

Eyes that received a cycle of monthly injections for first 3 months had better visual outcomes at 6 months than eyes that had *prn treatment* (three injection monthly = 0.66 logMAR to 0.33 logMAR *vs prn* treated = 0.91 logMAR to 0.66 logMAR); however, there was no significant difference at 12 months. There were few reported complications; there was only one case each of retinal detachment,[28] RPE rip,[24] and low grade iridocyclitis.[30]

These pooled 12-month data suggest that visual outcomes with bevacizumab treatment are better than other available options for myopic CNV. Cumulative data indicates that a mean of 1.56 injections is sufficient to stop the activity of myopic CNV. Under these circumstances, treatment with bevacizumab on a *prn* basis seems more logical than a cycle of three injections. Nonetheless, the recurrence of CNV is often difficult to assess in myopic CNV because of associated atrophic changes and the small size of the lesion. However, the long-term effects of bevacizumab on RPE atrophy remain unknown.

Currently, there are three ongoing clinical trials for the treatment of myopic CNV with bevacizumab, either alone or in combination with other therapeutics (clinicaltrials.gov). The results of these studies are pending.

Angioid streaks

Angioid streaks are linear breaks in the Bruch's membrane. These streaks may be an ocular manifestation of systemic conditions, such as pseudoxanthoma elasticum, Paget's disease, or sickle cell haemoglobinopathies. The most common complication of angioid streaks is the development of CNV and consequent impairment of vision. This phenomenon occurs in 72–86% of patients, and more than half of these patients present with bilateral CNV.[39] Angioid streaks usually affect young people and may have a profound effect on their working life. The natural history of CNV associated with angioid streaks is an irreversible deterioration of central vision. In most cases, this leads to legal blindness because of macular scarring and the development of a large central scotoma.

Therapeutic options

Therapeutic interventions such as laser photocoagulation, PDT, and surgery have shown variable success at preserving vision. New anti-angiogenic agents have opened up some alternatives for treatment of CNV secondary to angioid streaks.

Photodynamic therapy There are conflicting results for the treatment of angioid-streak-related CNV with PDT with verteporfin. In the short term, visual stabilisation and improved visual acuity of 1.37 lines have been reported at 8 months after PDT.[40,41] Browning *et al*[40] presented a minimal decrease of mean visual acuity from baseline in 16 eyes from 20/100 to 20/125 after a follow-up of 12 months in a study group of subfoveal CNV, whereas four out of seven eyes in the juxtafoveal CNV group progressed to a subfoveal location during the follow-up of 12 months. Other studies with longer follow-up also report enlarged CNV or disciform lesions in most patients with poor visual acuity of 20/600.[42,43] A study

Table 3 Visual outcomes after treatment of angioid-streak-related CNV with anti-angiogenic agents

Type of study	*Author(s)*	*Bevacizumab*	*Tx regimen*	*No. of eyes*	*Previous tx*	*Visual acuity (logMAR)*		*Mean follow-up (months)*	*Mean no. of txs*
						Initial	*Final*		
Case report	Apte[46]	1.25 mg/0.05 ml	3× inj. 6 weeks apart	1	Nil	0.54	0.18	6	1 cycle
Case report	Derriman *et al*[48]	1.25 mg/0.05 ml	3× inj.4–6 weeks apart	1	Nil	0.58	0.44	6	1 cycle
Case report	Japiassu *et al*[50]	1.25 mg/0.05 ml	stat + prn	1	PDT + laser	0.7	0.2	4	1
Case series	Finger *et al*[49]	1.25 mg/0.05 ml	stat + prn	16	4 eyes PDT	0.68	0.48	8	2.4
Case series	Rinaldi *et al*[52]	1.25 mg/0.05 ml	stat + prn	5	2 eyes PDT	0.72	0.42	6	1.4
Case series	Bhatnagar *et al*[47]	1.25 mg/0.05 ml	stat + prn	9	5 eyes IVTA + PDT; 1 eye had PDT	1.26	1.17	6	1.8
Case report	Teixeira *et al*[53]	1.25 mg/0.05 ml	stat + prn	1	Nil	2	0.18	3	2
Case series	Wiegand *et al*[54]	1.25 mg/0.05 ml	stat + prn	9	Nil	0.38	0.33	19.3	1.3
Prospective case series	Neri *et al*[51]	1.25 mg/0.05 ml	stat + prn	11	Nil	0.56	0.26	23.8	3.5

Tx, treatment; PRN, pro re nata; PDT, photodynamic therapy; IVTA, intravitreal triamcinolone.

with longer mean follow-up of 26.1 months on 15 eyes (10 with subfoveal, 5 with extra- or juxtafoveolar CNV) showed that the mean visual acuity decreased from 20/32 to $<20/200$ in nearly half the patients and only 13% was noted to have $\geqslant 20/63$ at final follow-up.[44]

Anti-angiogenic agents Owing to the rarity of this condition, single case reports are the prevalent source of treatment outcome data. Intravitreal bevacizumab (1.25 mg/0.05 ml) was used in all reports except for one, wherein pegaptanib sodium (0.3 mg/0.09 ml) was administered.[45] All reports indicate an improvement of vision in the short term (Table 3).[46–54] The longest follow-up is approximately 2 years (range: 3–24 months). There are several interesting trends among studies of angioid-streak-related CNV treatment with anti-angiogenic agents. Gains in vision and the mean number of injections were not significantly different between patients with naïve lesions and those with earlier treated eyes. There was also no difference in outcome after a cycle of three monthly injections when compared with *prn* administration. The mean number of injections administered in the treatment of angioid-streak-related CNV was higher than those for myopic CNV and lower than those for AMD CNV. Most studies reported decreased or absent leakage at the end of the follow-up. No injection-associated complications were reported.

The current evidence indicates that anti-angiogenic agents are the only treatment that might help patients with angioid-streak-related CNV. However, long-term studies are necessary to understand the full potential and adverse events of these treatments, particularly for co-morbidities such as pseudoxanthoma elasticum.

Angioid-streak-related CNV is aggressive and has a high rate of recurrence. These patients must be strongly encouraged to self-monitor their vision with Amsler charts and immediately report any visual distortion, even after initiation of anti-VEGF therapy. The area of CNV may be small, and OCT evidence of subretinal fluid may be the first sign of disease when a patient presents with a recurrence, even before angiographic evidence is obvious. Thus, for the first time, there is a useful therapy for this cohort of patients who harbour an aggressive disease that is often bilateral and blinding.

Inflammatory eye disease

CNV is a well-documented complication of posterior uveitis and white dot syndrome, with and without inflammation. Within this group of inflammatory diseases, CNV is a major sight-threatening complication, and patients with subfoveal CNV have the most guarded prognosis.[55,56]

Therapeutic options

Subfoveal CNV in various inflammatory chorioretinal disorders often responds to systemic,[57] periocular, or intraocular corticosteroid therapy. When this approach

Table 4 Visual outcomes after bevacizumab treatment of inflammatory CNV

Clinical condition	*Type of study*	*Author(s)*	*Bevacizumab dose (mg)*	*Treatment regimen*	*No. of eyes*	*Earlier treatment*	*Visual acuity (logMAR)*		*Mean follow-up (mo.s)*	*Mean no. of treatments*
							Initial	*Final*		
PIC[a]	Prospective case series	Chan *et al*[71]	1.25	0, 1, 2 m inj: repeat cycle if leakage at 3 months	4	1 eye had PDT	0.47	0.17	6	1 cycle
	Retrospective case series	Mansour *et al*[73]	1.25–2.5	variable (prn/3 inj + prn)	15	Steroids: systemic + local	0.49	0.27	3	2.2
	Case report	Rosen *et al*[76]	1.25	stat	1	1 eye had PDT	0.54	0.18	12	1
	Retrospective case series	Adan *et al*[70]	1.25	stat	3	None	0.53	0.28	7	1
POHS[b]	Retrospective case series	Mansour *et al*[73]	1.25–2.5	Variable (prn/3 inj + prn)	13	Steroids: systemic + local	0.73	0.61	3	1.5
	Retrospective case series	Schadlu *et al*[74]	1.25	stat	28	21 eyes had PDT	0.65	0.43	'6	1.8
	Case report	Adan *et al*[70]	1.25	stat	1	None	1	0.1	10	1
Multifocal choroiditis	Retrospective case series	Mansour *et al*[73]	1.25–2.5	Variable (prn/3 inj + prn)	15	Steroids: systemic + local	0.59	0.32 ± 0.343		1.4
	Retrospective case series	Adan *et al*[70]	1.25	stat	2	None	0.44	0.23	6	1
	Retrospective case series	Tran *et al*[75]	1.25	stat + prn	6	Systemic steroids/ immunosuppression/ PDT	0.63	0.47	7.5	2
VKH[c]	Retrospective case series	Mansour *et al*[73]	1.25–2.5	Variable prn/3 inj + prn)	5	Steroids: systemic + local	0.79	0.52	3	1.4
	Retrospective case series	Tran *et al*[75]	1.25	stat + prn	1	Systemic steroids/	0.18	0.1	6	2
Serpiginous/bird shot choroiditis	Retrospective case series	Mansour *et al*[73]	1.25–2.5	Variable prn/3 inj + prn)	6	Steroids: systemic + local	0.83	0.65	3	1.3
	Retrospective case series	Tran *et al*[75]	1.25	stat + prn	1	Systemic steroids/ immunosuppression	0.3	0.18	6	6
	Retrospective case series	Adan *et al*[70]	1.25	Stat	2	None	1	0.8	6	1.5
	Retrospective	Tran *et al*[75]	1.25	stat + prn	2	Systemic steroids/ immunosuppression	1.15	0.74	7.5	3.5
Toxo-plasmosis/ tuberculosis/ sarcoidosis	Retrospective	Mansour *et al*[73]	1.25–2.5	Variable (prn/3 inj + prn)	8	Steroids: systemic + local	0.67	0.34	3	1.1
	Case report	Guthoff and Goebel[72]	1.5	0, 2, 4 months	1	PDT + IVTA[d]	1	0	13	1 cycle

[a]PIC, punctate inner choroidopathy.
[b]POHS, presumed ocular histoplasmosis syndrome.
[c]VKH, Vogt Kayanagi Harada syndrome.
[d]IVTA, intravitreal triamcinolone.

fails, additional therapies have included laser photocoagulation,[58–60] PDT,[61,62] and submacular surgery,[63] with limited success.

Anti-inflammatory and immunosuppressive agents
Corticosteroids have been used in the treatment of inflammatory CNV. Mechanisms of intravitreal corticosteroids include reduction of retinal capillary permeability by increasing the activity and/or density of tight junctions in the retinal capillary endothelium,[64] inhibition of the VEGF gene expression, inhibition of the VEGF metabolic pathway,[65] and suppression of intracellular adhesion molecule-1 (ICAM-1)-mediated leucocyte adhesion to vessel walls.[66] Corticosteroids help keep vision stable, but increase the incidence of cataracts and glaucoma.

Photodynamic therapy Several studies have reported a beneficial effect of PDT in subfoveal and juxtafoveal inflammatory CNV. Stabilised or improved vision occurred in 70–92.3% of cases reported in retrospective studies.[67,68] One study reported on 13 multifocal choroiditis with panuveitis and subfoveal CNV patients who received PDT and reported stabilisation of vision over a 12-month follow-up.[62] A prospective study after a combination of intravitreal triamcinolone and PDT therapy reported stabilised or improved vision in 92.9% of patients at the end of 1 year.[69]

Anti-VEGF agents Seven studies have reported on the use of anti-VEGF therapy for CNV that is secondary to inflammation (Table 4).[70–76] Data pooled from these studies are derived from the treatment of 110 eyes. Although the inflammatory disease process varies between diseases, a sub-analysis reveals that the visual outcomes for the treatment of naïve eyes (mean gain of 0.28 logMAR) is better than for earlier treated eyes (0.25 logMAR). In most studies, inflammatory CNV responded favourably after a single dose of bevacizumab, especially in the treatment of naïve eyes. With few exceptions,[71,73] most studies have used *prn* regimens for treating CNV. Both *prn* and monthly injection for first 3 months schedules have shown favourable outcomes. No injection-related complications have been reported. Intravitreal injection of bevacizumab seems to be effective for treating extrafoveal, juxtafoveal, and subfoveal CNV, with no additional risk of exaggerated inflammatory response to the drug. Although the limited number of patients with CNV secondary to intraocular inflammation makes it difficult to carry out a prospective, randomised study of the effectiveness of anti-VEGF therapy, our literature analysis suggests that primary treatment with bevacizumab is useful to preserve vision in these patients.

Table 5 Visual outcomes following anti-VEGF treatment (tx) for idiopathic CNV

Type of study	*Author(s)*	*Agent (mg)*	*Tx regimen*	*No. of eyes*	*Patients*	*Prior tx*	*Visual acuity*		*Mean follow-up (mo.s)*	*Mean No. of txs*	*CNV Closure: follow up time and %*
							Initial	*Final*			
Retrospective	Mansour *et al*[73]	1.25–2.5	variable(prn/3 inj +prn)	11	NA	Nil	0.84	0.46	3	1.4	2.6 ± 0.9 weeks
Prospective	Chan *et al*[71]	1.25	0,1,2 m inj: repeat cycle if leakage at 3 months	9	9	6 eyes had PDT	0.54	0.16	6	1 cycle	At 3 months 100% closure
Retrospective	Mandal *et al*[30]	1.25	stat +prn	32	32	3 eyes had PDT	1.02	0.49	4.2	1.7	NA[a]

[a]NA, not available.

Idiopathic CNV

For many young patients with CNV, there is no apparent cause. These cases are diagnosed as ICNV.[77] The natural history of idiopathic subfoveal CNV is not necessarily associated with a profound loss of vision. Lesions of one disc area or smaller at the time of initial fluorescein angiography are more likely to be associated with a final visual acuity of 20/60 or better and less likely to be associated with a final visual acuity of 20/200 or worse.[77]

Therapeutic options

Several studies have shown PDT to be effective in ICNV.[78] In up to 94% of cases, PDT stabilises vision at the end of 1 year.[78] Similar results are reported at the end of 2 years in small case studies.[79] Visual outcomes after other treatments, such as TTT, submacular surgery, or macular translocation, have not been satisfactory.[80]

We pooled data from three studies that successfully treated a total of 52 ICNV eyes with bevacizumab.[30,71,73] Overall, visual acuity changed from an initial mean value of 0.8 logMAR to 0.33 logMAR at the end of a mean 5.1 months follow-up. One study[71] used three monthly injections in nine eyes, and the other two used a *prn* regimen.[30,73] Most cases respond favourably within 1 month and required a mean of 1.55 injections per eye (range: 1.4–1.7). Though the average follow-up was short, no injection-related, long-term complications were reported. One eye developed anterior uveitis, which was successfully treated with topical steroids (Table 5).

Other causes of CNV

Numerous other case reports have described the successful use of bevacizumab for the treatment of non-AMD CNV. These include studies with a short follow-up for CNV secondary to Best disease,[81] vitelliform degeneration,[82] choroidal oesteoma,[83] and pseudotumour cerebri.[84]

Discussion

Owing to the low incidence of non-AMD-related CNV, randomised controlled trials are difficult to conduct. Owing to the rarity of the CNV conditions described, we did not limit our study to only those that met the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement writing standards.[85] Consequently, this review examined all possible published reports, and included case series on small numbers of patients, with variable follow-up periods. Our aim was to report trends and that would be relevant to the treatment of patients with these rare diseases.

The cumulative evidence provides good indication of successful 'off-label' use of bevacizumab for the improvement of visual outcomes in non-AMD CNV patients. These conditions require very few injections and respond well to OCT-guided *prn*-treatment schedules. On the basis of PRONTO[86] study for AMD, several investigators have tried a cycle of three injections for these conditions. However, the outcomes of single injections followed by *prn* were similar to those given a loading dose of three injections.

Similarly, although the follow-up periods of these studies are short, there are no significant differences in the rates of complications for this therapy in non-AMD CNV, compared with AMD CNV. We recommend centralised reporting of the effects of treatment and side effects of these rare conditions to ensure improved understanding of the best-treatment strategy.

Conclusions

Definitive conclusions are not possible when examining retrospective studies with small sample sizes, variable follow-up, and a lack of a standard phenotypic and anatomical CNV classification. Regardless, consistently favourable outcomes have been reported with intravitreal bevacizumab treatment of non-AMD-related CNV.

Conflict of interest

The authors declare no conflict of interest.

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