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CLINICAL STUDY

Intravitreal ranibizumab for the treatment of choroidal neovascularisation secondary to angioid streaks

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Abstract

Aims **To assess the medium to long-term efficacy and safety of intravitreal ranibizumab for the treatment of choroidal neovascularisation (CNV) secondary to angioid streaks (AS).**

Methods **A total of 12 eyes of nine patients treated with intravitreal ranibizumab (0.5 mg in 0.05 ml) for CNV secondary to AS were retrospectively identified. Efficacy of treatment was determined by changes in best-corrected LogMAR visual acuity (BCVA) and optical coherence tomography. Changes with respect to baseline BCVA were defined as improved or reduced with a gain or loss of more than 10 letters, respectively, or stable if remaining within 10 letters.**

Results **Over a mean follow-up of 21.75 months (range: 1–54), patients received mean 5.75 (range: 2–15) intravitreal ranibizumab injections per affected eye. BCVA improved in three eyes (25%), stabilised in eight eyes (66.67%), and deteriorated in one eye (8.33%). There was no significant change in central retinal thickness (CRT) over the follow-up period ($P = 0.1072$). No drug-related systemic side effects were recorded.**

Conclusion **The long-term treatment of CNV secondary to AS with intravitreal ranibizumab showed a stabilisation in CRT and an improvement or stabilisation of BCVA. The absence of systemic side effects was reassuring. Further long-term prospective studies are required to validate these findings.**

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Introduction

Angioid streaks (AS) represent linear breaks or dehiscences in an abnormally fragile or calcified Bruch's membrane and may be due to systemic associations such as pseudoxanthoma elasticum (PXE), Ehlers–Danlos syndrome, or sickle cell disease, although up to 50% may have no detectable systemic disease association.[1,2] Choroidal neovascularisation (CNV) is one of the commonest complications of AS and has been reported to occur in 70–86% of patients, with up to 71% developing CNV in the fellow eye.[2] AS are rare with a reported annual incidence of AS-related CNV at 0.057 per 100 000 population in United Kingdom.[3] The natural history of AS-associated CNV typically leads to significant visual impairment with most eyes progressing to legal blindness.[4–8] Laser photocoagulation of juxtafoveal or extrafoveal CNV secondary to AS has demonstrated high recurrence rates with varied success.[2,8] Photodynamic therapy (PDT) has been used as an alternative treatment method for both juxtafoveal and subfoveal CNV; however, long-term visual outcomes have generally remained poor.[9–11] Recently, ranibizumab, a humanised Fab fragment of a monoclonal antibody that binds to and inhibits the action of all isoforms of vascular endothelial growth factor (VEGF) A, was licensed for the treatment of CNV secondary to age-related macular degeneration (AMD), and became the only anti-VEGF

recommended by the National Institute of Health and Clinical Excellence in the UK for the treatment of CNV secondary to AMD.[12]

Recent studies have suggested that the use of intravitreal ranibizumab is efficacious in the treatment of CNV secondary to causes other than AMD, such as pathologic myopia or ocular histoplasmosis.[13,14] Similar reports exist of outcomes of bevacizumab treatment in eyes with CNV secondary to non-AMD causes.[15] The use of intravitreal ranibizumab for the treatment of AS-related CNV has been reported to be more effective when compared with previous reports of laser photocoagulation or PDT, with most eyes demonstrating a stabilisation or improvement in visual acuity. However, most of these studies are limited to single case reports, small numbers of patients or have limited/short follow-up.[16–22]

We report a retrospective case series that assesses the medium to long-term efficacy and safety of intravitreal ranibizumab in patients with CNV secondary to AS.

Materials and methods

Nine patients with CNV secondary to AS confirmed on fundus fluorescein angiography (FFA) and treated with intravitreal injections of ranibizumab under the care of one consultant were retrospectively identified. Details of best-corrected LogMAR visual acuity (BCVA), dates of ranibizumab injections, and any documented complications were retrieved from patient records. Central retinal thickness (CRT) was measured using either the Stratus optical coherence tomography (OCT) model 3000 (Carl Zeiss Meditec Inc., Dublin, CA, USA) or Topcon 3D OCT 1000 (Topcon, Newbury, UK).

The primary end points were the percentage of eyes with stable or improved BCVA at last follow-up and the occurrence of any systemic drug-related side effects. Changes with respect to baseline BCVA were defined as improved or reduced with a gain or loss of >10 letters, respectively, or stable if remaining within 10 letters.

The intravitreal ranibizumab injections were performed in accordance with the Royal College of Ophthalmologists (RCOphth) Intravitreal Injection Procedure Guidelines.[23] Ranibizumab (Lucentis, Novartis Pharma SAS, Huningue, France; 0.5 mg in 0.05 ml) was injected 3.5–4 mm posterior to the limbus with a 30-gauge half-inch needle. All patients gave informed consent to treatment with intravitreal ranibizumab injections. The initial treatment with one injection of ranibizumab was performed on eyes with active CNV as evidenced by the presence of subretinal or intraretinal fluid on OCT, with or without retinal haemorrhage and leakage on FFA. Patients were followed up approximately 4 weeks after the initial injection and then at regular intervals as decided by the treating ophthalmologist. The decision of repeat treatment was based on continuing disease activity indicated by decreasing VA, new retinal haemorrhage, and/or subretinal or intraretinal fluid on OCT and/or leakage or enlargement of CNV on FFA.

Results

A total of 12 eyes of nine patients were treated with intravitreal injections of ranibizumab for CNV secondary to AS (Table 1). Mean age was 55.5 years (range 43–77) at initial treatment with ranibizumab, and six of the nine patients were male. Six of the nine patients had AS secondary to PXE and three had no systemic association identified. Four patients were treated previously for CNV with PDT. The choroidal neovascular membrane was extrafoveal in two eyes (16.67%), juxtafoveal in two eyes (16.67%), and subfoveal in eight eyes (66.67%). Follow-up from initial treatment was mean 21.75 months (range: 1–54). Patients received mean 5.75 (range: 2–15) intravitreal ranibizumab injections per affected eye during the follow-up period. The mean interval between intravitreal ranibizumab injections was 2.97 months (range: 0.93–25.97).

Mean BCVA at baseline was 0.40 (range: -0.12–1.06) and at last follow-up was 0.36 (range: -0.1–1.24) ($P=0.6066$). At last follow-up (at a mean of 21.75 months) BCVA improved by >10 letters in three eyes (25%), stabilised to within 10 letters of baseline BCVA in eight eyes (66.67%), and deteriorated by >10 letters in one eye (8.33%). The eye (patient 2) that experienced a decline in BCVA of 25 letters over the follow-up period demonstrated foveal retinal pigment epithelium (RPE) atrophy on fundus examination. There was an injection-free interval of 26 months after which a new CNV occurred in this eye requiring treatment. The eye that had a decline in BCVA of nine letters (patient 9) had been treated with PDT 64 months before the first intravitreal ranibizumab injection.

There was no significant change in CRT over the follow-up period ($P=0.1072$). Mean CRT at baseline was 275 μm (range: 191–451) and at last follow-up was 236 μm (range 175–412). Baseline and last follow-up OCT measurements were performed on the same OCT machine for all patients except for patient 2 where baseline measurements were on Stratus OCT model 3000 and last follow-up measurements were on Topcon 3D OCT 1000.

No systemic side effects were recorded within the follow-up period following the use of intravitreal ranibizumab. Patient 2 developed a small conjunctival haemorrhage at the injection site in the left eye following the third intravitreal ranibizumab injection. This resolved without any sequelae and the patient went on to have five further intravitreal ranibizumab injections to the same eye.

Table 1 Patient data

Patient	*Age (years)*	*Diagnosis*	*Eye*	*PDT*	*Initial BCVA*	*Initial OCT–CRT*	*No of ranibi-zumab injections*	*Final BCVA*	*Final OCT–CRT*	*Duration of follow-up (months)*	*Change in BCVA*	*Change in OCT–CRT*	*CNVM position*
1	43	Idiopathic	OD	2	0.64	451	3	0.64	269	54	0.00	−182	Subfoveal
			OS	1	0.92	446	12	0.54	247	24	−0.38	−199	Subfoveal
2	54	PXE	OD	0	−0.12	200	15	0.02	225	28	0.14	25	Subfoveal
			OS (a)	0	−0.08	193	3	0.42	221	51	0.50	28	Subfoveal
			OS (b)	0	0.40	191	5	0.42	221	22	0.02	30	Subfoveal
3	51	Idiopathic	OS	0	0.54	260	4	0.66	231	25	0.12	−29	Subfoveal
4	52	PXE	OD	1.5	0.00	392	8	0.10	412	22	0.10	20	Juxtafoveal
5	54	PXE	OS	0	0.00	268	2	−0.10	223	15	−0.10	−45	Extrafoveal
6	51	PXE	OS	0	0.28	238	2	0.10	175	7	−0.18	−63	Subfoveal
7	77	Idiopathic	OD	2	0.52	223	5	0.02	253	18	−0.50	30	Subfoveal
8	62	PXE	OS	0	0.18	193	5	0.00	206	14	−0.18	13	Extrafoveal
9	56	PXE	OD	0	0.80	212	3	0.58	196	2	−0.22	−16	Juxtafoveal
			OS	1	1.06	306	2	1.24	189	1	0.18	−117	Subfoveal

Abbreviations: BCVA, best-corrected LogMAR visual acuity; CNVM, choroidal neovascular membrane; CRT, central retinal thickness (μm); OCT, optical coherence tomography; OS (a), initial subfoveal CNV; OS (b), new subfoveal CNV; PDT, number of photodynamic therapy treatments; PXE, pseudoxanthoma elasticum.

Discussion

Although rare, AS cause significant visual impairment due to CNV. CNV is reported to occur in up to 86% of patients with serious visual consequences, particularly as it affects people of working age.[1,2] Studies have shown that the majority of untreated patients with CNV secondary to AS develop a significant visual impairment resulting in legal blindness.[4–8] Although various treatment options are available for AS-related CNV, to date most published trials have involved either laser photocoagulation or PDT. Studies on the treatment of juxtafoveal and extrafoveal lesions by laser photocoagulation have provided variable results. Although some studies have shown favourable outcomes with the stabilisation of vision in the short-term, others have demonstrated a significant deterioration.[2,4,8] Despite this short-term variability in vision, all studies have demonstrated a high rate of CNV recurrence, with one study reporting CNV recurrence in 77% of eyes.[2,8] Studies of PDT for the treatment of CNV secondary to AS have also shown disappointing long-term results. Despite promising results with the stabilisation of vision in the short-term, longer follow-up demonstrated a progressive loss of visual acuity.[9–11] One study reported a limitation of visual loss after 1 year, particularly in those with subfoveal lesions; however, further follow-up at 2 years showed progressive visual decline.[9,10] The natural history of AS-associated CNV has a tendency towards disease progression and poor visual outcomes, which makes treatment difficult. Existing treatments have been shown to be poorly efficacious in the long-term. Of the current treatments available for AS-related CNV, anti-VEGFs have been shown to be the most promising. There are relatively few studies that have assessed the efficacy of intravitreal ranibizumab to treat CNV secondary to AS because the condition is so rare. Traditionally, clinical practice around the treatment of CNV secondary to causes other than AMD has been based on studies carried out on patients with AMD. There is significant evidence demonstrating the efficacy of intravitreal ranibizumab in either improving or stabilising visual acuity in patients treated for CNV secondary to AMD.[24–27]

Previous studies have demonstrated that ranibizumab has a prolonged effect in either stabilising or improving vision in CNV secondary to AS.[13,14,16–22] Mimoun *et al*[18] published a retrospective case series of 35 eyes with mean follow-up of 24.1 months. Mean BCVA improved or stabilised in 30 eyes (85.7%), macular thickness decreased or stabilised in 18 eyes (51.5%), and no further leakage on FFA was observed in 23 eyes (65.7%).[18] Ladas *et al*[19] reported a prospective case series of 15 eyes with mean follow-up of 16 months. Mean BCVA and retinal thickness improved significantly, with 93.3% showing an improvement or stabilisation in vision.[19] Vadalà *et al*[20] reported a series of nine patients who received 0.3 mg ranibizumab injections with a mean follow-up of 14 months. Mean visual acuity increased significantly with eight (88.9%) of the nine patients demonstrating an improvement or stabilisation in vision. There was also a significant reduction in mean OCT macular thickness at last follow-up.[20] Finger *et al*[21] published a 12-month prospective study of seven eyes and demonstrated a significant improvement in visual acuity from baseline with a reduction in mean CRT and leakage from active CNVs.

This study is one of the largest retrospective interventional case series with one of the longest follow-up periods of patients treated with intravitreal ranibizumab for CNV secondary to AS. Mimoun *et al*[18] reported that BCVA improved or stabilised in 85.7% of eyes; however, they defined significant changes in BCVA as 15 letters or more compared with baseline. This is comparable to the 91.6% who lost 10 or fewer letters in

our series. The only eye in our series which experienced a decline in BCVA of 25 letters had a corresponding foveal RPE atrophy which confounded the outcome. It is not possible to determine what role previous treatment with PDT may have in confounding visual outcome. There was no significant difference in CRT from baseline to last follow-up. In our study, patients received mean 5.75 intravitreal ranibizumab injections over mean follow-up of 21.75 months. Mimoun *et al*[18] treated each eye with mean 5.7 intravitreal ranibizumab injections over a mean follow-up of 24.1 months. Ladas *et al*[19] treated each eye with mean 7.1 intravitreal ranibizumab injections over a 16-month period. Vadalà *et al*[20] treated patients with mean five intravitreal ranibizumab injections (which included a loading dose of three monthly injections); however, mean follow-up was only 14 months. Finger *et al*[21] treated each eye with 12 intravitreal ranibizumab injections over the same number of months. In our study, there was a mean interval between intravitreal ranibizumab injections of 2.97 months, which suggests that intravitreal ranibizumab may be effective when given pro re nata, with treatment guided by CNV activity.

We recognise that this study has the limitations of any retrospective case series with its inherent selection bias and precludes generalised statements about the use of intravitreal ranibizumab for the treatment of all CNV secondary to AS. However, five eyes (42%) were followed up for 2 years or more, a time period in which existing treatments have demonstrated a progressive decline in visual acuity. Although a prospective randomised controlled trial would be the gold standard to determine the safety and efficacy of ranibizumab for the treatment of CNV secondary to AS, this is unlikely due to the low disease prevalence. However, intravitreal ranibizumab shows promise when compared with the disease progression in eyes treated with existing therapies.

In conclusion, intravitreal ranibizumab was tolerated well by patients in this series and appears to be a safe and effective treatment for CNV secondary to AS.

Summary

What was known before

- CNV is a common complication of AS and untreated has a poor visual prognosis.
- Treatment of CNV secondary to AS with laser photocoagulation and PDT has poor long-term visual outcomes.

What this study adds

- The long-term treatment of CNV secondary to AS with intravitreal ranibizumab appears to be safe and effective.

Conflict of interest

Mr Winfried Amoaku has undertaken research sponsored by Bausch and Lomb, Novartis and Pfizer. He has also received travel grants from Allergan, Novartis, and Pfizer, speaker honoraria from Allergan, Novartis, and Pfizer, and participated in Advisory Boards of Allergan, Bayer, Novartis, and Pfizer. Dr Mital Shah declares no conflict of interest.

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