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CLINICAL STUDY

Early response of retinal angiomatous proliferation treated with intravitreal pegaptanib: a retrospective review

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Abstract

Aims **To evaluate the early functional and anatomical responses to intravitreal pegaptanib in patients with retinal angiomatous proliferation (RAP).**
Methods **Retrospective review of consecutive patients newly diagnosed with RAP treated with intravitreal pegaptanib (0.3 mg). Examination at baseline and 12 weekly intervals included refraction protocol best corrected visual acuity (BCVA), fluorescein angiography (FA), and optical coherence tomography (OCT). At intervening 6 weekly visits a reduced protocol assessment included BCVA and OCT.**
Results **A total of 16 eyes of 16 patients (12 female, mean age 76.0 years) with RAP at baseline (15 stage 3, one stage 2) were treated. One patient had poor response, losing 20 ETDRS letters after one injection and was switched to photodynamic therapy combined with intravitreal triamcinolone. Mean BCVA ($n=15$) was baseline 45 ± 11 (mean $\pm$ SD) letters, 12 weeks 43 ± 14 letters, 24 weeks 40 ± 14 letters; the reduction from baseline to 24 weeks was statistically significant ($P=0.04$). Vision remained stable defined as ±15 letters of baseline BCVA in 13 (87%) of patients 2 (13%) lost >15 letters. Mean OCT central foveal thickness (CFT) ($n=13$) was: baseline $325\pm123\,\mu m$, 12 weeks $343\pm130\,\mu m$, 24 weeks $321\pm115\,\mu m$; difference at 24 weeks was not statistically significant ($P=0.9$). A pigment epithelial detachment was present in 12 cases; height was reduced in 10 cases at 24 weeks. Persistent leakage on FA was seen in 13 out of 15 cases at 24 weeks.**
Conclusion **Early results of treatment of RAP with intravitreal pegaptanib suggest some stabilizing effect on this normally progressive disease.**
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Keywords: pegaptanib; intravitreal; retinal angiomatous proliferation; macugen

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Introduction

Retinal angiomatous proliferation (RAP) is a form of neovascular age-related macular degeneration (AMD) in which intraretinal neovascularisation (stage I) progresses to subretinal neovascularisation with or without serous pigment epithelial detachment (PED) (stage II), followed by choroidal neovascularisation (CNV) (stage III).[1,2] It is estimated to comprise 10–15% of all newly diagnosed neovascular AMD and 30% of occult CNV.[3] The presence of RAP is correlated with worse visual prognosis[3] and is commonly bilateral with nearly all patients developing RAP in the fellow eye within 3 years.[4]

Effective treatment for RAP has yet to be established. Thermal laser may have a role for extrafoveal stage I and II RAP[5] but reported outcomes are poor in more advanced disease.[6] Surgical ablation of feeder vessels has been described in a small number of patients with stage II RAP[7] but appears ineffective with a high rate of recurrence.[8] Case series of patients treated with anecortave acetate[9] or photodynamic therapy (PDT) with verteporfin as monotherapy have not shown favourable functional or anatomical outcome.[10] PDT has been applied more successfully when combined with intravitreal triamcinolone (IVTA) injected simultaneously or up to 14 days before or after.

Case series with 12-month follow-up report 83–89% visual stabilisation and 35–37% visual improvement[11–13] but with important side effects of raised intraocular pressure (IOP), cataract, and retinal pigment epithelial tears.[14,15]

The intravitreal vascular endothelial growth factor (VEGF) antagonists ranibizumab and pegaptanib have been shown to reduce vascular leakage and improve the functional outcome in patients with CNV.[16–18] Uncontrolled studies suggest that bevacizumab may also be effective.[19,20] Outer retinal ischaemia with localised VEGF production has been postulated as a possible mechanism for the development of intraretinal neovascularisation in RAP.[2] Two case series have shown promising 3 month data on treatment of RAP with intravitreal bevacizumab.[21,22] At the time of writing, there are no published reports of the effectiveness of ranibizumab or pegaptanib in the treatment of RAP. We report 6-month follow-up of a case series of patients with RAP treated with intravitreal pegaptanib.

Materials and methods

Retrospective analysis of a consecutive case series of patients diagnosed with RAP and treated with 6 weekly intravitreal pegaptanib at a regional tertiary referral treatment centre.

Examination at baseline and 12 weekly intervals included refraction protocol best corrected visual acuity (BCVA) measured by an optometrist and recorded as letters read at 2 m on ETDRS charts with standard illumination, IOP, and slit-lamp fundus biomicroscopy. Stereoscopic colour fundus photography, fluorescein angiography (FA), and optical coherence tomography (OCT) were also performed.

At intervening 6 weekly visits, a reduced protocol assessment included BCVA using the previous refraction, IOP, and OCT.

Diagnosis of RAP

Diagnosis was confirmed by two senior doctors (PML, SM) with experience of grading colour photographs and angiograms within the UK Network of Reading Centres and classified according to the system proposed by Yannuzzi *et al*.[2] The following features specific to the diagnosis and staging of RAP were required to include the patient in the study. With indocyanine green (ICG) angiography being performed in some cases to support the diagnosis.

1. Features on stereoscopic colour photographs:

- early lesions: intraretinal haemorrhage, feeder retinal vessels with right angle turns and dilated tips
- later lesions: serous pigment epithelial detachment (PED) and exudates

2. Features on stereoscopic angiography:

- small zone(s) of early intense hyperfluorescence ('hot spot') identified as intraretinal on stereo FA and/or ICG showing leakage throughout the series
- feeder vessel from retinal circulation best seen on arteriovenous phase of dye transit phase, retina-retina anastomosis or chorioretinal anastomosis
- serous PED and evidence of CNV

Zeiss VISUPAC software was used to measure the greatest linear diameter (GLD) of the lesion, (RAP vessels and any associated serous or fibrovascular pigment epithelial detachment (FPED)).

OCT imaging was performed using the Stratus OCT3 system (Carl Zeiss, software version 4.0). The Fast Macular Thickness acquisition protocol was used and central foveal thickness (CFT) was recorded. Correct identification of the retinal boundaries by the software was verified.

All patients underwent an intravitreal injection with 0.3 mg (0.09 ml) pegaptanib by pars plana under sterile conditions. Hand movement perception and pulsation of the central retinal artery were confirmed after injection. Patients were contacted by telephone 3 days after each injection to confirm there were no adverse reactions and scheduled for follow-up visits at 6-week intervals.

A paired *t*-test was performed for analysis of BCVA and retinal thickness over time. *P*-values <0.05 were considered statistically significant.

Results

A total of 16 eyes of 16 patients were treated, (summary data, Table 1). Twelve patients were female. The mean age was 76.0 years (range 58–87). One eye was graded as RAP stage 2, the remainder as stage 3. Symptom duration before first treatment ranged from 12 to 68 weeks (median 25 weeks). In each of 13 cases, the fellow eyes had previously been affected by neovascular AMD and had poor visual acuity; six of these had one or more chorioretinal anastomosis. One patient had a poor response after the first injection with loss of 20 ETDRS letters and increased retinal thickness and was switched to PDT combined with IVTA (sample case 2). This patient was excluded from quantitative analysis at 24 weeks. Baseline OCT information was not available in two patients who had their first treatment in private sector hospitals where this was not performed as routine. Quantitative measures on FA was also not possible on baseline images for these patients but diagnosis could be confirmed. One patient did not have any follow-up

angiography due to presumed allergy; diagnosis was made on referral angiogram. Fourteen patients received all four injections before their 24-week visit; one patient had only three injections as he failed to attend one appointment. All patients completed 24-week follow-up.

Mean BCVA ($n = 15$) was: baseline 45 ± 11(mean ± SD) letters, 12 weeks 43 ± 14 letters, 24 weeks 40 ± 14 letters; the reduction from baseline to 24 weeks was statistically significant ($P = 0.04$ paired t-test). Vision remained stable defined as ±15 letters of baseline BCVA in 13 (87%) of

Table 1 Summary patient data

Patient	*RAP Stage*	*Baseline*				*12 weeks*		*24 weeks*				*No. of injections*
		Vision (ETDRS letters)	*OCT CFT (μm)*	*PED*	*Lesion GLD (mm)*	*Vision (ETDRS letters)*	*OCT CFT (μm)*	*Vision (ETDRS letters)*	*OCT CFT (μm)*	*PED*	*Lesion GLD (mm)*	
1	2	63	258	Yes	1.99	69	263	68	242	Reduced	0.56	4
2	3	36	232	No	7.35	NA	NA	22	281	No	FA not performed	3
3	3	34	461	Yes	NA	29	572	31	511	Stable	FA not performed	4
4	3	42	391	Yes	6.02	34	411	29	411	Reduced	5.84	4
5	3	67	172	Yes	6.57	64	240	61	301	Reduced	6.6	4
6	3	60	164	Yes	6.15	56	333	53	278	Reduced	5.25	4
7	3	33	602	Yes	7.01	29	604	40	527	Stable	8.04	4
8	3	50	358	Yes	2.27	57	295	48	285	Reduced	2.25	4
9	3	31	425	Yes	4.69	37	363	33	343	Reduced	5.94	4
10	3	44	NA	No	NA	43	203	44	272	No	4.03	4
11	3	43	308	Yes	7.42	43	332	23	405	Reduced	7.19	4
12	3	44	275	Yes	5.31	45	311	36	250	Reduced	4.71	4
13	3	42	NA	Yes	NA	21	349	21	264	Stable	6.51	4
14	3	44	337	Yes	5.49	59	202	54	132	Reduced	5.47	4
15	3	42	245	Yes	6.24	40	201	41	204	Reduced	5.63	4
16	3	63	399	Yes	4.58	43[a]	863[a]	61	238	Reduced	5.73	1

NA = not available.
[a]Results at 6 weeks.

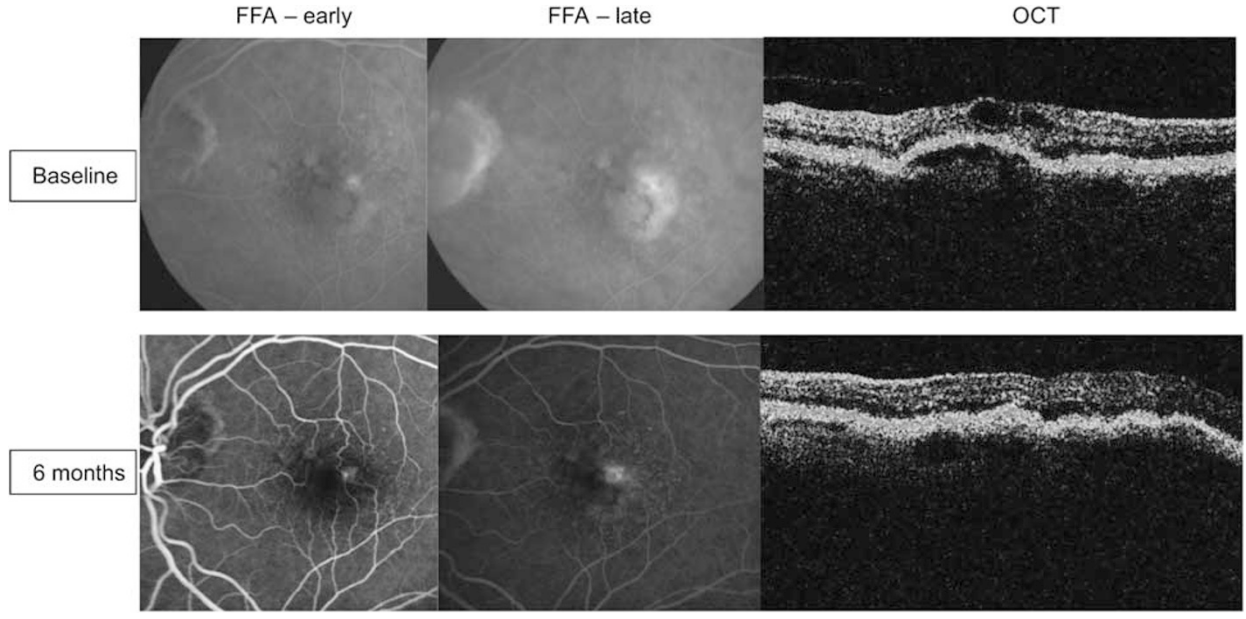

Figure 1 Stage 2 RAP with serous pigment epithelial detachment.

patients. Five patients (33%) remained within 5 letters of baseline, 2 (13%) gained >5 letters, 8 (53%) lost >5 letters of whom 2 (13%) lost >15 letters.

Mean OCT CFT ($n=13$) at baseline was $325\pm123\,\mu m$, $343\pm130\,\mu m$ at 12 weeks, and $321\pm115\,\mu m$ at 24 weeks. At 24 weeks, the difference was not statistically significant ($P=0.9$ paired t-test). In six patients CFT increased by a mean of 77 μm (range 20–129); in seven patients, CFT decreased by mean of 74 μm (range −16 to −205). OCT confirmed a PED in 12 cases. At 24 weeks, the PED height was reduced in 10 of these cases.

Review of the fluorescein angiograms showed that in 13 out of 15 cases the lesion showed signs of persistent leakage at 24 weeks. In the remaining two cases the lesion did not show any signs of active leakage at 24 weeks. In two cases the GLD of the active lesion increased by 1.03 and 1.25 mm. In the remainder there was a small reduction at 24 weeks (mean −0.44 mm). The difference did not reach statistical significance ($P=0.5$).

No adverse reactions occurred during the study period.

Sample cases

Two cases are presented, one illustrating a good response and also more detail on the patient with a poor response and change of treatment. Most lesions remained stable.

Patient no. 1 (Figure 1): an 80-year-old female presented with recent reduction of vision to 6/18 (63 letters) with diagnosis of RAP. Baseline FA and OCT showed a RAP complex and a serous PED with baseline CFT of 258 μm. Six months after injection there was minimal residual leakage on FA and CFT was 242 μm. BCVA was a little better (68 letters).

Patient no. 16 (Figure 2): a 75-year-old female with a 2-month history of reduction in vision in her left eye. The fellow eye had mature fibrosed CNV. Baseline BCVA was 63 ETDRS letters. FFA and OCT showed RAP vessels and a large FPED with baseline CFT 399 μm.

At 6 weeks, vision had dropped to 39 letters and area involved by FPED enlarged. CFT had increased to 863 μm. The treatment was switched to PDT and IVTA. At 6 months from baseline, vision had improved again to 61 letters, CFT reduced to 238 μm.

Discussion

We report the early response to intravitreal pegaptanib therapy in RAP, an uncommon variant of AMD. Eighty seven per cent of cases maintained vision within 15 letters of baseline with 13% gaining ⩾5 and 53% losing ⩾5. There was variability in response to treatment as measured by CFT on OCT with roughly equal numbers experiencing increased and decreased thickness. The height of the PED reduced in the majority of cases. There

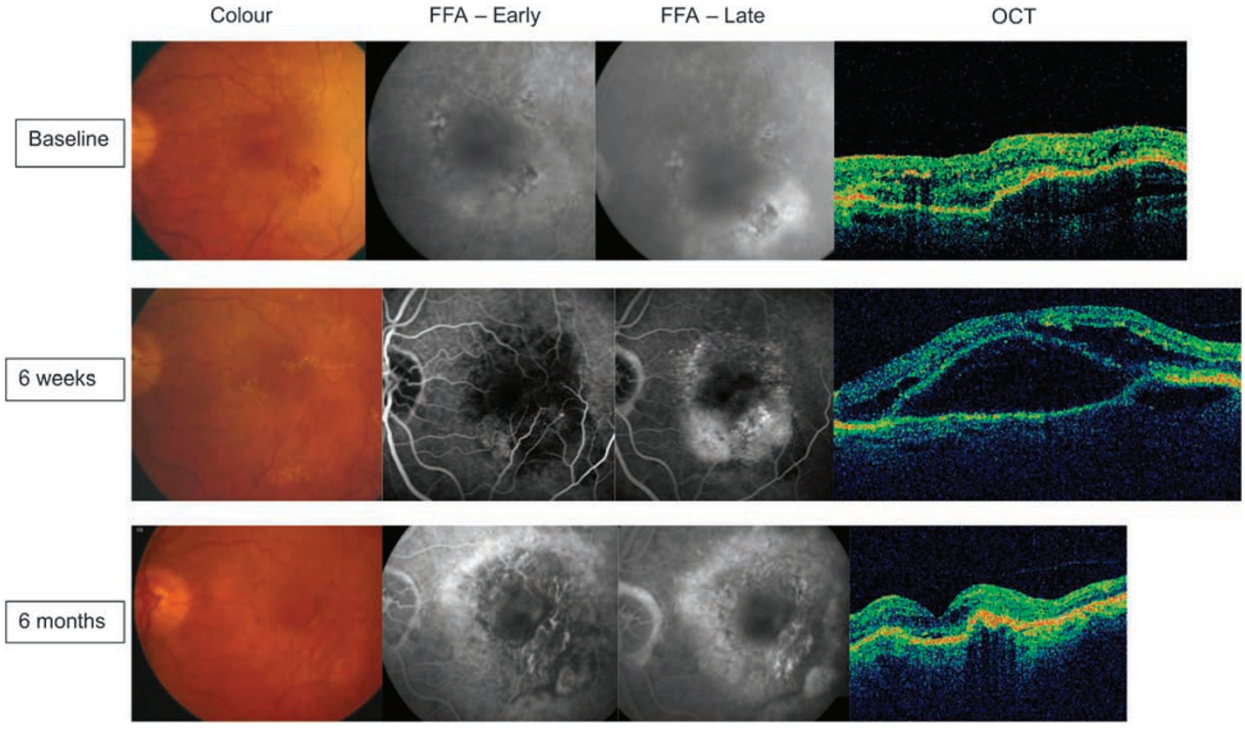

Figure 2 Stage 3 RAP with fibrovascular and serous pigment epithelial detachment.

Table 2 Three-month visual acuity outcomes in studies of anti-VEGF for RAP

	No.	*RAP stage 1*	*RAP stage 2*	*RAP stage 3*	*Visual loss ⩾3 Snellen lines (%)*	*Visual improvement (%)*	*Total stabilization (within 3 Snellen lines) or improvement (%)*
Bevacizumab (Joeres *et al*[22])	16	0	16 (not classified separately)		0	50 (gain ⩾2 Snellen lines)	100
Bevacizumab (Meyerle *et al*[21])	23	11	10	2	5.9	29.4 (gain ⩾3 Snellen lines)	94.1
Pegaptanib (current paper)	16	0	1	15	18.8	6.3 (gain ⩾3 Snellen lines)	81.3

was some reduction of leakage on FA. Complete resolution of leakage was achieved in only two patients after 24 weeks of treatment. There was a statistically significant trend toward a small reduction of five letters in BCVA but no significant change on OCT CFT.

In future, intravitreal anti-VEGF agents may become the most common therapy for neovascular AMD. Their usage in the context of RAP requires more study, preferably of large numbers, but this is likely to prove difficult due to the small numbers of cases seen even in large treatment centres, such as ours. RAP lesions, where identified, have been excluded from the large, multicentre, randomised controlled clinical trials of pegaptanib and ranibizumab.

At the time of writing, two case series have reported the use of intravitreal bevacizumab and the possible beneficial effects at 3-month review. In the case series reported by Meyerle *et al*, out of 17 patients, vision loss was reported in only one case and five eyes (29.4%) had better acuity. There was a significant reduction in mean CFT. Change in angiographic leakage was not reported.[21] Joeres *et al*[22] studied 16 patients, eight eyes (50%) gained ⩾2 lines visual acuity from baseline to month 3; none of the eyes lost ⩾2 lines. There was a significant reduction in central macular thickness but no morphological change in the feeder vessel and closure was not achieved in any case.

Comparison of these case series with our patients shows a high level of stabilisation of vision at 3 months with both drugs but pegaptanib does not appear to show the same level of visual improvement (Table 2). Both series of bevacizumab also report significant reduction in mean CFT. This may indicate a higher degree of efficacy for bevacizumab but the patient characteristics are not comparable. In our series, only one case was stage 2 RAP, the rest stage 3. In Meyerle *et al*[21] case series, 48% of patients had stage 1 disease and only 9% stage 3. Joeres *et al* stated that 'no differentiation is made between stage 2 and stage 3 lesions' so the series may have been a mix of stage 2 and 3 disease. Previous reports indicate that treatment of RAP at earlier stages may lead to better anatomical and functional outcomes; when the vascular complex is well established, anatomical closure is difficult to achieve.[23]

In conclusion, intravitreal anti-VEGF treatment with pegaptanib appears to have an effect on vision and CFT in patients with RAP. Against the background of a generally aggressive natural history, treatment appears to maintain function at 6 months in the majority of patients, although the effect appears to be limited and somewhat variable. Long-term follow-up at 12 and 24 months would show if this effect is maintained. Large randomized, controlled trials are also required to establish optimum treatment but may prove difficult to organise.

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