CLINICAL STUDY

Anti-VEGF therapy for choroidal neovascularisation previously treated with photodynamic therapy

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Abstract

Purpose   This interventional, non-comparative case series assessed the outcome of intravitreal pan-anti-vascular endothelial growth factor (VEGF) agents in eyes with persistent or reactivated choroidal neovascularisation (CNV) following previous treatment with photodynamic therapy (PDT).
Methods   Baseline assessments including best-corrected visual acuity, fluorescein angiography (FFA), and optical coherent tomography (OCT) were performed. Intravitreal ranibizumab and/ or bevacizumab were administered on a PRN basis, guided by changes in visual outcome and OCT findings. The follow-up period was at least 6 months.
Results   Twenty-five subjects with predominantly classic CNV, previously treated with PDT (mean 1.84 PDT sessions) showed reactivation or persistent CNV. The mean interval between PDT and intravitreal anti-VEGF treatment was 18.32 months (1–48 months); and patients received an average of 3.2 injections over a 6-month period. The mean change of visual acuity following PDT was −10.12 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (54.36 ± 15.79–44.24 ± 17.32 letters). Following anti-VEGF therapy, the mean change in visual acuity at 3 and 6 months were +1.76 and +0.72, respectively. The proportion of subjects with stable vision (loss of ⩽15 letters) was 96% at 3 months and 88% at 6 months; the proportion of subjects who showed improved vision (⩾15 letters) was 8% at 3 months and 4% at 6 months.
Conclusions   Anti-VEGF agents stabilised the visual outcomes of eyes previously treated with PDT. However, the proportion of patients who showed improved vision in this group was smaller than the proportion reported in subjects with treatment-naive lesions.

Introduction

Choroidal neovascularisation (CNV) secondary to neovascular age-related macular degeneration (AMD) cases are classified into angiographic subtypes depending on the proportion of the classic component into predominantly classic, minimally classic, and occult CNV.[1] The aim of this treatment is to ablate or modulate CNV to minimise damage to adjacent structures. The Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP report 1) study reported in 1999 that 61% of subjects with predominantly classic CNV treated with Verteporfin (Visudyne: Novartis Pharmaceuticals Corp., East Hanover, NJ, USA) photodynamic therapy (PDT) lost fewer than 15 letters at 1 year, compared with 46% of subjects treated with placebo.[2] Since then, PDT has been the treatment of choice for predominantly classic lesions.

Management of neovascular AMD is changing with advances in understanding its pathophysiology.[3] Since the recent development of pharmacological agents that block vascular endothelial growth factor (VEGF) in CNV, well-conducted trials have shown that intravitreal ranibizumab, an anti-VEGF monoclonal antibody fragment that blocks all isoforms of VEGF-A, provides a much more effective

alternative to the traditional techniques, which were at best able to stabilise (but rarely improve) visual acuity.[4,5] The 12-month results of the 2-year phase III trial on monthly intravitreal ranibizumab therapy *vs* PDT for predominantly classic CNV showed that 96.4% of the 0.5 mg ranibizumab group lost fewer than 15 letters, compared with 64.3% in the PDT arm (ANCHOR study).[5] In this study, subjects in the PDT arm were allowed to cross over to ranibizumab therapy at 18 months or later when intravitreal ranibizumab became the standard care for all subtypes of CNV secondary to AMD.[6]

In daily practice, bevacizumab, a full-length monoclonal anti-VEGF antibody, became available for neovascular AMD before ranibizumab was authorised,[7] and some subjects undergoing PDT opted for it, although it has not been licensed for intraocular use.

In this study, we report the outcomes of the use of ranibizumab and bevacizumab in consecutive subjects with AMD-related predominantly classic CNV previously treated with PDT; we compared the outcomes with those reported in patients who crossed over in the ANCHOR 2-year trial.

Methods

This study was approved by the local ethics committee; informed consent for the use of intravitreal ranibizumab and the associated risks, benefits, and treatment alternatives was obtained from all subjects. Intravitreal bevacizumab was used as a treatment option before ranibizumab became available in the NHS. Informed consent for the 'off-label' use of this drug was also obtained.

Consecutive subjects that presented with persistent or recurrent CNV following previous treatment with PDT for predominantly classic CNV were identified from a database maintained by the Laser and Retinal Research Unit, King's College hospital for anti-VEGF therapy. The database has been in operation since February 2007.

Inclusion criteria were: (1) age ⩾50 years; (2) clinical diagnosis of wet AMD; (3) predominantly classic CNV treated with PDT showing persistent or new activity; and (4) best-corrected visual acuity of 24–73 letters on the Early Treatment Diabetic Retinopathy Study (EDTRS) chart.[8] Active CNV (persistent or recurrent) was defined as recent disease progression, as evidenced by a recent decline in vision, with new or persistent subretinal or intraretinal fluid on optical coherent tomography (OCT), an increase in lesion size >10% and persistent leak as evidenced on fundus fluorescein angiogram (FFA), or new haemorrhage. Only one eye of each patient was included in the study.

Exclusion criteria included CNV from causes other than AMD (myopia, angioid streaks, choroidal rupture,

chorio-retinal scarring, etc). Subjects with permanent structural damage at the fovea with limited visual potential (assessed by the treating physician) were excluded from the study. Patients were not excluded for pre-existing systemic health problems.

Ocular examination

All subjects underwent complete ophthalmic examination, including slit-lamp bio microscopic examination of the anterior segment, intraocular pressure measurement, and dilated fundoscopic examination of the posterior pole at every visit. FFA was carried out before the commencement of PDT and before initiation of anti-VEGF therapy; following this, it was performed at the discretion of the treating physician. OCT examinations were performed at every visit using a STRATUS OCT (Carl Zeiss, Meditec). The fast macular thickness map protocol was used for quantitative measures of the central macular thickness (CMT) and macular volume.

Treatment options

Photodynamic therapy
Subjects received standard fluence verteporfin PDT in accordance with the TAP protocol (verteporfin infusion over 10 min at a dose of 6 mg/m^2; activating light applied 15 min after start of infusion at a wavelength of 689 nm, light dose of 50 J/cm, and fluence of 600 mW/cm^2) at baseline. Subjects were followed up every 12 weeks, and FFA was repeated to assess activity. All subjects with reactivation of CNV were included in this case series. Subjects who were started on PDT at the time anti-VEGF treatment became available were given the option to switch to anti-VEGF therapy if there was persistent disease activity without permanent structural damage to the fovea (as judged by the treating physician).

Intravitreal ranibizumab/bevacizumab therapy
After administration of topical anaesthesia, ranibizumab 0.5 mg/0.05 ml or bevacizumab 1.25 mg/0.05 ml was injected using a 30-G needle through a pars plana approach under aseptic conditions. Subjects self-administered a topical antimicrobial agent (1% ofloxacin ophthalmic solution) 4 times daily for 3 days after treatment. All subjects were followed up monthly. Re-injection of anti-VEGF agent was performed if visual acuity had deteriorated and (a) the OCT showed persistent or new fluid, (b) new haemorrhage was noted, (c) the lesion size increased by ⩾10%.

Outcome measures

The primary efficacy end point was the proportion of subjects who lost fewer than 15 ETDRS letters at 6 months after initiation of anti-VEGF therapy. The change in visual outcome from the baseline (before the initiation of the first PDT session) was a secondary efficacy end point. Additional exploratory end points were the comparative outcomes of sequential therapy of bevacizumab followed by ranibizumab, *vs* ranibizumab monotherapy in subjects previously treated with PDT. The results were compared with the crossover group in the 2-year report of the ANCHOR study, in which subjects previously treated with PDT were allowed to cross over to the ranibizumab arm and were monitored for 6 months.

Multiple linear regression analysis was carried out to assess the factors that influenced the outcome. Factors assessed included visual acuity, CMT, macular volume before commencement of anti-VEGF therapy, number of PDT sessions, thickness of the subfoveal subretinal tissue at 6 months, presence of intraretinal cysts, and subretinal fluid, and macular fluid (defined as a combination of intraretinal fluid and subretinal fluid).

Results

Patient demographics

Twenty-five consecutive subjects with predominantly classic CNV who had been treated previously with PDT were included. The mean age was 79.84 ± 5.76 years (range 71–91 years). All subjects were Caucasian, with a comparable number of men (48%) and women (52%). There were four subjects with coexistent ocular pathology (two with non-proliferative diabetic retinopathy and two with primary open-angle glaucoma), and two subjects were pseudophakic.

Baseline characteristics

The mean total pre-PDT greatest linear diameter of the lesion was 1832 μm (median 1850 μm; range 716–3000 μm). The mean number of PDT sessions was 1.84 (range: 1–5 sessions). No subjects received any combination treatments at baseline. Before treating with anti-VEGF regimen, one had intravitreal triamcinolone, two had sub tenons triamcinolone, and three had orbital floor triamcinolone as treatment for persistent activity of neovascular membrane. None had undergone laser treatment.

Anti-VEGF therapy

The interval between last PDT and start of anti-VEGF regime was 18.32 months (1–48 months). Eleven subjects were initiated on intravitreal bevacizumab and then switched to ranibizumab when the drug became available. This cohort received a mean of 1.8 intravitreal bevacizumab (1–4) and 0.4 ranibizumab (1–4). The remaining patients ($n = 14$) received ranibizumab monotherapy, with a mean of 3.6 injections (1–5). The mean number of anti-VEGF injections for the whole cohort was 3.2 in 6 months (1–5). Subanalysis of the pattern of injections revealed that 18 (72%) received the first three injections on a monthly basis, followed by a PRN approach (3 + PRN approach), whereas seven (28%) received PRN therapy throughout the treatment period.

Changes in visual acuity

Mean baseline visual acuity before PDT was 54.36 ± 15.79 ETDRS letters (35–85); at initiation of anti-VEGF treatment, mean visual acuity was 44.24 ± 17.32 ETDRS letters (13–80). There was a mean change in post-PDT visual acuity of -10.12 ETDRS letters during a mean follow-up of 18.32 months. Table 1 shows the mean

Table 1 Outcomes of anti-VEGF therapy in CNV previously treated with PDT

	Anti-VEGF onset (n = 25)	Month 1 (n = 25)	Month 2 (n = 25)	Month 3 (n = 25)	Month 6 (n = 25)
Mean VA (ETDRS)	44.24	46.32	46	46	44.96
Mean change in VA (ETDRS) since baseline (pre PDT)	−10.12	−8.06	−8.36	−8.36	−9.40
Mean change in VA (ETDRS) since the start of anti-VEGF regimen	Not applicable	+2.06	+1.76	+1.76	+0.72
CMT	328 μm	270 μm	283 μm	275 μm	281 μm
CFV	7.47 mm^3	6.92 mm^3	7.35 mm^3	7.72 mm^3	8.17 mm^3
Percentage losing < 15 letters	NA	100%	100%	96%	88%
Percent gaining ⩾ 15 letters	NA	none	none	8%	4%

CFV, central foveal volume; CMT, central macular thickness; CNV, choroidal neovascularisation; NA, not applicable; PDT, photodynamic therapy; VA, visual acuity; VEGF, vascular endothelial growth factor.

change in visual acuity after commencement of anti-VEGF therapy.

The mean change of visual acuity at 6 months in the group that had sequential therapy of bevacizumab followed by ranibizumab was −1.82 (−19 to +11), compared with +1.04 ETDRS letters (−16 to +17) in the group treated with ranibizumab only. There was no statistical difference in the mean change in visual acuity in the 3+PRN group at 6 months (+1.05 (−19 to +17)) compared with the PRN group, in whom mean change was −0.14 ETDRS letters (−8 to +7). The visual acuity of two patients who developed retinal pigment epithelial tear dropped significantly (−15 and −16 ETDRS letters, respectively), after initially gaining vision from anti-VEGF treatment.

Tomographic changes

The mean CMT had decreased by 46.78 μm (−237 μm to +97 μm) 6 months after initiation of anti-VEGF therapy, but there was no significant change in macular volume. The mean thickness of the subretinal tissue (using callipers) was 114.44 μm at 6 months (range 54–222 μm). At the 6-month follow-up, intraretinal fluid persisted in 28% of the patients, subretinal fluid persisted in 20%, and macular fluid (intraretinal fluid plus subretinal fluid) persisted in 4% of the patients. Hence 56% had no fluid.

Factors influencing outcomes

Multiple logistic regression showed that baseline visual acuity ($P = 0.04$) and subfoveal subretinal tissue ($P = 0.04$) influenced the final visual outcome. Figure 1 shows the correlation between visual acuity change and subretinal tissue thickness ($r^2 = 0.5$).

Comparison of results to ANCHOR the crossover group

Table 2 shows the comparison of our baseline characteristics and results with that of the ANCHOR crossover group ($n = 50$).[6]
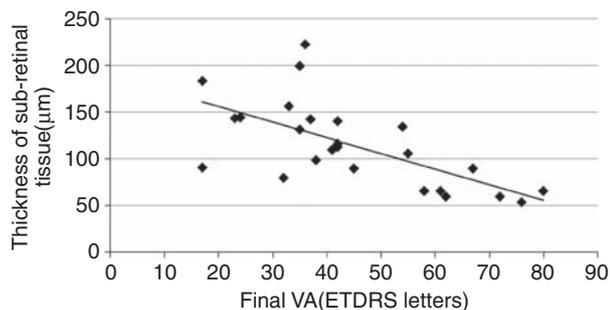

Figure 1 Correlation of final visual acuity (ETDRS letters) to thickness of subretinal tissue.

Figure 2 shows that there are no significant differences in the pattern of visual outcomes in the two groups following PDT as well as after anti-VEGF therapy. The gain in visual acuity is minimal with most subjects ending up with poorer vision compared with their baseline pre-PDT visual acuity.[6]

Complications

Two patients developed an extrafoveal RPE rip at the edge of the fibrotic lesion. There were no cases of increase in RPE atrophy, and no cases of endophthalmitis or uveitis.

Discussion

Several studies have shown the therapeutic efficiency and safety profile of intravitreal pan-VEGF-A inhibitors (ranibizumab and bevacizumab) in the management of CNV secondary to neovascular AMD.[4–7] Most studies have opted for an OCT-guided regimen, based on the Prospective OCT Imaging of Patients with Neovascular AMD Treated with Intraocular Ranibizumab (PrONTO) study; these studies have shown stabilisation of visual acuity in more than 90% of the subjects and improvement in visual acuity in over 35% of the subjects.[8,9] Studies assessing the outcome of a combination of anti-VEGF agents with PDT in various protocols have shown similar results. For example, FOCUS, a Phase I/II clinical study, investigated the safety and efficacy of ranibizumab in combination with PDT compared with PDT alone in subjects with predominantly classic wet AMD.[10] Results at 12 months showed that 94.3% of those given 0.3 mg of ranibizumab and 96.4% of those given 0.5 mg lost fewer than 15 letters, as compared with 64.3% of those in the PDT group. Visual acuity improved by 15 letters or more in 35.7% of the 0.3 mg group and 40.3% of the 0.5 mg group, as compared with 5.6% of the PDT group. Mean visual acuity increased by 8.5 letters in the 0.3 mg group and 11.3 letters in the 0.5 mg group, and it decreased by 9.5 letters in the PDT group.

In this case series, we evaluated outcomes of treatment with ranibizumab and bevacizumab in CNV that had been previously treated with PDT. We found that 88% of patients lost fewer than 15 letters, and visual acuity improved by 15 letters or more in 4% at 6 months. The mean visual acuity increased by +0.72 letters. These results show that the visual outcomes of this group are worse than that in treatment-naive lesions treated with anti-VEGF monotherapy or a combination of anti-VEGF and PDT.

Our results are similar to that obtained at 6 months in the 50 subjects who crossed over to the ranibizumab arm from the PDT arm in the ANCHOR study.[6]

Table 2 Comparison of outcomes of present series *vs* the ANCHOR crossover group

	Anchor crossover group (n = 50) Crossover to Ranibizumab at 18 months	Present series (n = 25)
Age mean (SD)	76.3 (7.9)	79.84 (5.76)
Mean interval between PDT and anti-VEGF regimen	18 months	18.32 months
Baseline mean VA	43.9	54.36
VA ⩾45	26	20
VA <45	24	5
CNV lesion subtype:		
Predominantly classic *n* (%)	50 (100%)	25 (100%)
No. of PDT sessions	3.8	1.84
Mean VA at the onset of anti-VEGF regimen	38.5	44.24
Follow-up duration	6 months	6 months
Mean number of injections	3.3	3.2
Frequency of injections	monthly	OCT-guided
Dosage of anti-VEGF (in 0.05 ml)	0.3 mg ranibizumab	0.5 mg ranibizumab/1.25 mg bevacizumab
Mean VA 6 months after starting anti-VEGF regimen	38.2	44.96
Mean VA gain since anti-VEGF regimen	+ 0.2	+ 0.72
Mean change in VA since baseline (pre-PDT)	−5.7 ETDRS letters	−9.4 ETDRS letters
Change in mean CMT	NA	−47.36 μm

ANCHOR, Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularisation in AMD; CMT, central macular thickness; CNV, choroidal neovascularisation; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherent tomography; PDT, photodynamic therapy; SD, standard deviation; VA, visual acuity; VEGF, vascular endothelial growth factor.

The ANCHOR crossover group received a dose of 0.3 mg/0.5 ml every month, whereas in our study, the subjects received 0.5 mg/0.05 ml in an OCT-guided regimen. In addition, our cohort also had better baseline mean vision (pre-PDT), better mean visual acuity at the start of anti-VEGF therapy and had less number of PDT sessions (Table 2). The reasons for better baseline mean visual acuity in our series could be attributed to the fact that 10% of the crossover patients in the ANCHOR study had recurrent CNV after previous laser treatment, which could have affected the overall baseline visual acuity whereas the patients in our series were treatment-naive patients before photodynamic therapy.

The differences in outcome of post-PDT cases compared with the original ANCHOR study may be related to the PDT-induced collateral damage to choriocapillaries, RPE, and retina.[11] Lesions treated with PDT usually result in retinal pigment epithelial atrophy and/or subretinal fibrosis.[12] We analysed several factors that might influence final visual outcome including baseline visual acuity (pre-PDT), pre-anti-VEGF visual acuity, size of lesion, number of PDT treatments, thickness of subfoveal subretinal tissue, macular volume, central retinal thickness, area of angiographic leakage, number of anti-VEGF agents, and the number of treatments with anti-VEGF agents. Of all these factors, only baseline visual acuity (pre-PDT) and the thickness of subfoveal subretinal tissue influenced the final visual outcome. Recent OCT classification of morphological appearance of CNV have indicated that the subretinal hyper-reflective band corresponds to fibrosis.[13]
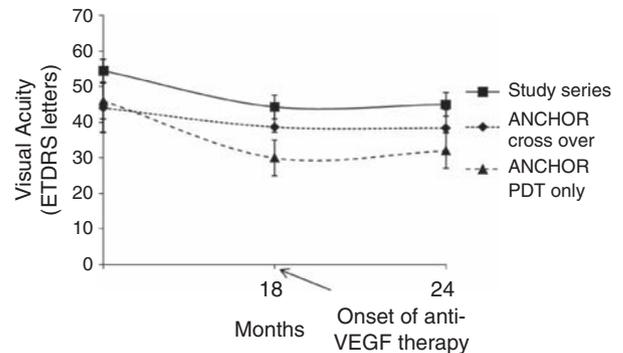

Figure 2 Comparison of VA outcome with ANCHOR cross over and PDT only patients.

Therefore, the thicker the subfoveal subretinal tissue, the worse the final visual outcome.

It is important to differentiate this study from studies that have assessed the outcome of combining anti-VEGF agents with PDT in various protocols.[10,14] The combination treatments have shown better visual outcomes. In PDT, micro vascular occlusion induces inflammation and hypoxia and the expression of VEGF, which could lead to CNV persistence and recurrence. For that reason, synergistic inhibition of VEGF with PDT provides a multipronged attack on the CNV.[15,16] However, this study shows that, unlike the combination therapy, sequential therapy of PDT followed by anti-VEGF at a later date does not provide a similar synergistic effect. This may be because anti-VEGF agents can only modulate the CNV by decreasing the

PDT-induced VEGF drive and have minimal or no effect on the atrophic and fibrotic changes induced by PDT in the long-term.

This study showed that it is safe to administer anti-VEGF agents into PDT-treated eyes. There were two cases of RPE rip at the extrafoveal edge of the fibrosis. This may be a response to the tangential force on the fibrosis caused by sudden decrease in fluid after anti-VEGF therapy. None of the subjects showed an increase in RPE atrophy.

This study provides a real-life experience of using anti-VEGF agents in eyes previously treated with PDT. Our study has a few weaknesses. The most important limitation was the lack of a control group treated with PDT alone. However, as the ANCHOR study clearly showed the superior outcomes of intravitreal ranibizumab over PDT, it is not ethically appropriate to continue treating subjects with PDT.[5] Second, our 6-month follow-up period is relatively short in the context of the natural history of the disease; long-term treatment efficacy remains to be determined. Third, the optimal dosage, number, and frequency of intravitreal ranibizumab/bevacizumab injections in eyes previously treated with PDT remain uncertain. Our study showed that the subjects who received the first three injections on a fixed monthly schedule did not fare better than the group treated on OCT-guided PRN basis from the first visit. We also noted no difference in outcome between the group treated with ranibizumab alone and the group treated with a combination of bevacizumab and ranibizumab. It may be argued that the small sample size may have skewed the results in the subgroup analysis. However, our study outcomes compared very well with the crossover group of a well designed randomised controlled trial (ANCHOR 2-year study). We conclude that activation of CNV in eyes previously treated with PDT can be treated safely with an OCT-guided regimen of intravitreal anti-VEGF agents. However, patients should be informed that the aim of anti-VEGF therapy is stabilisation of vision, and the likelihood of visual improvement is limited.

Conflict of interest

The authors declare no conflict of interest.

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