Bevacizumab for neovascular age−related macular degeneration in Chinese patients in a clinical setting

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Received: 2015-02-05   Accepted: 2015-07-10

Abstract

• **AIM:** To determine the outcome of non−investigational treatment with intravitreal bevacizumab (IVB) in neovascular age −related macular degeneration (AMD) patients.

• **METHODS:** Retrospective chart review of 81 eyes with neovascular AMD followed −up for at least 12mo and received 3−monthly loading IVB injections. Re−treat was based upon the individual clinician´s judgment. Best − corrected visual acuity (BCVA) and optical coherence tomography measurements of central foveal thickness outcomes were evaluated at 12, 24mo.

• **RESULTS:** Eighty−one eyes (of 75 patients) completed 12mo of follow−up and 44 eyes (of 41 patients) completed 24mo of follow −up. The mean baseline logMAR BCVA significantly improved from 0.94 ±0.69 to 0.85 ±0.68 at 12mo (P<0.001) and from 0.91±0.65 to 0.85±0.60 (P=0.004) at 24mo. The proportion of eyes that lost <15 logMAR letters at 12mo was 90.1% and at 24mo was 81.8%. IVB was effective in improving visual acuity in both treatment naïve and previous photodynamic therapy (PDT)−treated subgroups. Treatment naive patients required significantly fewer injections than patients with prior PDT. Multiple regression analysis identified that poorer baseline visual acuity was associated with greater improvement in visual acuity (P=0.015).

• **CONCLUSION:** Fewer injections in clinical practice may result in suboptimal visual outcomes compared with clinical trials of IVB in neovascular AMD patients. Poor baseline visual acuity and prior PDT treatment may also improve vision after IVB. The safety and durability of effect was maintained at 24mo.

INTRODUCTION

In recent years, the development of vascular endothelial growth factor (VEGF) inhibitors that can be intravitreally injected has revolutionized the therapeutic approach for neovascular age-related macular degeneration (AMD). Tightly controlled multicenter randomized controlled studies have convincingly shown the treatment benefits for neovascular AMD patients with ranibizumab (Lucentis, Genetech, San Francisco, California, USA), bevacizumab (Avastin, Genetech, San Francisco, California, USA) and aflibercept (Eylea, Bayer Healthcare Pharmaceuticals, Berlin, Germany)[1-5]. Ranibizumab is licensed for AMD since 2007 and aflibercept in 2012. Both drugs are approved by the National Institute for Health and Clinical Excellence in United Kingdom and the Hospital Authority in Hong Kong, whereas bevacizumab is not. Given the substantial higher costs of ranibizumab and aflibercept, many private patients still prefer off-label use of bevacizumab for AMD. Nevertheless, in clinical trials, rigid treatment and follow-up protocols are usually mandated and patients are recruited according to strict inclusion and exclusion criteria to ensure validity of results. Furthermore, a heavy treatment burden on all parties involved in routine clinical practice has led to dosing regimens that are less intensive than those used in clinical trials, such as the PrONTO and treat-and-extend regimens [6-7]. It is uncertain whether identical outcomes from clinical trials will be replicated in the wider community in everyday practice. Here, we describe the safety and efficacy of intravitreal bevacizumab (IVB) over 12-24mo of non-investigational treatment in a non-selected population of neovascular AMD patients.

SUBJECTS AND METHODS

The study was performed in accordance with the standards of the Declaration of Helsinki and was approved by the Institutional Review Board of the Hong Kong Sanatorium

and Hospital. Patients were informed about the off-label conditions of IVB. Women of childbearing age were also informed about the possible risks to the fetus and contraception was advised throughout the following 3mo after injection. At each post-injection visit, patients were monitored for ocular side effects [best-corrected visual acuity (BCVA), intraocular pressure (IOP) measurements, indirect ophthalmoscopy, slit-lamp biomicroscopy] and systemic side effects (medication changes, high blood pressure, signs of cerebrovascular accidents, myocardial infarctions or ischemia).

Since June 5th, 2006, every patients receiving anti-VEGF injection (ranibizumab and bevacizumab) in the injection room of the outpatient clinic at the Hong Kong Sanatorium and Hospital would have a prospectively designed audit form that the respective doctor had to fill out and then filed. Another injection logbook also recorded the date, patient name, and doctor name of every injection. The medical records of all such cases from June 5th, 2006 to December 17th, 2010 were reviewed. All Chinese patients >50y with provisional diagnosis of neovascular AMD followed-up for at least 12mo and received IVB injections were included in the study regardless of baseline visual acuity, choroidal neovascularization (CNV) size, location (subfoveal or juxtafoveal) and composition (classic lesions including both predominantly and minimally classic types, or occult lesions). In all patients, the baseline fluorescein angiography (FA) was independently assessed by two of the investigators (Ng DS and Tong JM) to confirm CNV leakage and lesion composition. Lesions obscured by severe subretinal haemorrhage were categorized as undetermined. The exclusion criteria were: 1) history of photodynamic therapy (PDT) or intravitreal triamcinolone (TA) during follow-up period after bevacizumab; 2) any form of combination therapy; 3) cataract extraction after bevacizumab; 4) CNV attributable to any cause other than AMD (such as myopic degeneration); 5) either polypoidal choroidal vasculopathy or retinal angiomatous proliferation confirmed by indocyanine green angiograph; 6) presence of comorbid ocular conditions, particularly diabetic retinopathy, that might compromise visual acuity.

All patients received a comprehensive baseline ophthalmological examination, including BCVA, IOP measurements, indirect ophthalmoscopy and slit-lamp biomicroscopy. The documented findings from Stratus optical coherence tomography (OCT) (Carl Ziess, Dublin, CA, USA) and FA were reviewed. BCVA was recorded in Snellen decimal values and converted to the logarithm of the minimal angle of resolution (logMAR) units. Visual acuity of counting fingers was equal to 2.30 logMAR units (decimal Snellen acuity of 0.005) and hand movement was equal to 2.70 (decimal Snellen acuity of 0.002). BCVA was converted to logMAR letters for standardization with the published results from clinical trials.

Details of the standard protocol for IVB injection have been reported previously [8]. The intravitreal doses of 1.25 mg bevacizumab was injected in an office setting by 8 ophthalmologists using 30-guage needle at 3.5-4 mm post-limbus. Prophylactic topical antibiotics were applied for a few days to 1wk after the injection. Bevacizumab injection was given at the baseline visit, with a fixed 4-6 weekly injection regimen for the next 2mo. No defined protocol for re-treatment was available, and the decision to re-treat was based upon the individual clinician's judgment on the presence of persistent subretinal fluid, new onset of macular hemorrhage, worsening visual acuity, increased retinal thickening by OCT and/or increased leakage of CNV assessed by FA.

At each follow-up visit, data were collected on the patients' BCVA, whether they received retreatment, OCT measurements (if available), adverse ocular and systemic events, and the date of visit. The visits closest to the time points at 1, 3, 6, 12, 18, 24mo were analyzed. Statistical analysis was performed using SPSS (SPSS Inc. Chicago, IL, USA). Two-tailed paired t tests were used to compare visual acuities between different time points and unpaired t tests for comparison of parametric continuous variables between subgroups. Categorical variables were compared using Chi-square test. Multivariate analysis by linear regression was performed to evaluate the association of pretreatment covariates including age, gender, prior treatment with PDT, CNV lesion type, greatest linear diameter (mm) of CNV, baseline BCVA, baseline central foveal thickness (CFT) measured by OCT and duration of symptoms (mo) as reported by patients. The mean BCVA change at 12, 24mo from baseline were chosen as the outcomes for multivariate analysis. A P value of <0.05 was considered statistically significant.

RESULTS

Of the 118 cases with CNV secondary to AMD, 81 eyes of 75 patients met the inclusion criteria with follow-up of 12mo. From these cases, 44 eyes (of 41 patients) completed 24mo of follow-up. The mean±standard deviation follow-up period for all included patients was 22.7±10.6mo. Patients' demographics and clinical characteristics are presented in Table 1.

The mean baseline BCVA in logMAR units of the 81 eyes was 0.94±0.69. This improved to 0.85±0.63 at the 3mo ($P<$ 0.001) (Figure 1A). The statistically significant improvement of visual acuity was maintained at 12mo ($P<0.001$), and the mean BCVA in logMAR units was 0.85±0.68 with a mean gain of 0.10±0.67 logMAR units from baseline. For the 44 eyes that completed 24mo of follow-up, the mean BCVA in logMAR units improved significantly from baseline 0.91±

Table 1 Demographics and clinical characteristics of neovascular AMD patients who completed 12 and 24mo of follow-up

	$\bar{x} \pm s, n\ (\%)$	
Parameters	12mo	24mo
No. of eyes	81	44
Male	41 (50.6)	20 (45.5)
Female	40 (49.4)	24 (54.5)
Age (a)	77.04±8.86	76.43±8.64
Past health		
Hypertension	46 (56.8)	20 (59.1)
Smoker	11 (13.6)	5 (11.4)
Taking antiplatelet drugs	13 (16.0)	6 (13.6)
Cerebrovascular accident	2 (2.5)	1 (2.3)
Past ophthalmic history		
Pseudophakic	51 (63.0)	28 (63.8)
Glaucoma	8 (9.9)	6 (13.6)
Duration of symptoms (mo)	5.7±5.2	5.6±5.3
Previous treatments		
Prior PDT treatment	20 (24.7)	16 (36.4)
Previous TA	1 (1.2)	1 (2.3)
Previous pars plana vitrectomy	4 (4.9)	4 (9.1)
FA findings		
CNV lesion size (MPS DA)	2.84±2.49	2.37±2.23
Classic type	8 (9.9)	5 (11.4)
Occult type	22 (27.2)	18 (40.9)
Juxtafoveal CNV	4 (4.9)	2 (4.5)
Treatment dosing and frequency		
Dose of 2.50 mg IVB	5 (6.2)	3 (6.8)
No. of patients required retreatment	36 (44.4)	25 (56.8)
No. of Injections	4.7±2.4	9.2±6.1

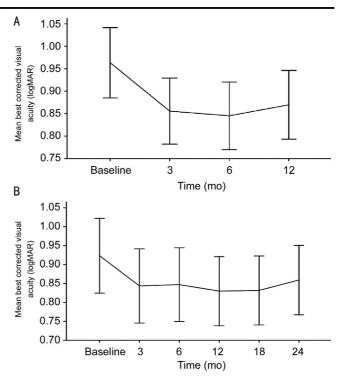MPS DA: Macular photocoagulation study disc areas.

Figure 1 Changes in the mean logarithm of the minimum angle of resolution (logMAR) BCVA following IVB treatment A: Eyes (n =81) that completed 12mo of follow-up; B: Eyes (n = 44) that completed 24mo of follow-up.
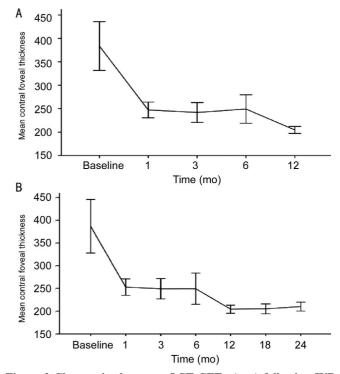

Figure 2 Changes in the mean OCT CFT (μm) following IVB treatment A: Eyes (n =81) that completed 12mo of follow-up; B: Eyes (n =44) that completed 24mo of follow-up.

0.65 to 0.82±0.60 at 12mo (P =0.002) and 0.85± 0.60 (P = 0.004) at 24mo (Figure 1B). The slight drop in vision from 12mo to 24mo was not statistically significant (mean change=0.03 logMAR units, P=0.085). The mean gain of BCVA at 24mo was 0.06 ±0.59 from baseline. The mean number of injections given during the 12mo and 24mo periods were 4.6 (range 3-10) and 9.2 (range 3-21), respectively. For comparison with clinical trials, visual acuity was converted into logMAR letters (Table 2). The number of eyes that gained >15 logMAR letters was 27 out of 81 eyes (33.3%) at 12mo and 12 out of 44 eyes (27.3%) at 24mo. The number of eyes that lost <15 logMAR letters at 12mo was 73 out of 81 eyes (90.1%) and at 24mo was 36 out of 44 eyes (81.8%).

The mean CFT at baseline was 310.82 μm and was decreased to 214.41 μm at 12mo (n =81) and 217.26 μm at 24mo (n =44). The mean reduction of CFT compared with baseline was statistically significant; 119.44 μm at 12mo (P = 0.001) and 116.73 μm at 24mo (P=0.026) (Figure 2).

The mean gain in BCVA in treatment naïve patients was 0.02±0.46 (P =0.025) and 0.06±0.69 (P=0.032) logMAR units at 12mo (n =61) and 24mo (n =28), respectively. The

mean gain in BCVA of the subgroup of patients with prior PDT was 0.10±0.15 (P=0.035) and 0.11±0.13 (P=0.044) logMAR units at 12mo (n=20) and 24mo (n=16), respectively. This subgroup required a mean of 6.6 injections during the first 12mo, which was significantly more than the treatment naïve group (mean injections=4.0, P=0.002). This statistically

Table 2 Comparisons of 1y results from clinical trials with the present study

Clinical trials	ANCHOR[2]	MARINA[1]	PIER[9]	PrONTO[6]	CATT (ranibizumab-monthly)[3]	CATT (bevacizumab-monthly)[3]	CATT (ranibizumab-as needed)[3]	CATT (bevacizumab-as needed)[3]	Present study
Eyes that lost <15 letters (%)	96.4	94.6	90.2	95.0	94.4	94.0	95.4	91.5	90.1
Eyes that improved by 15 or more letters (%)	40.3	33.8	13.1	35.0	34.2	31.3	24.9	28.0	33.3
Mean BCVA change (letters)	+11.3	+7.2	-0.2	+9.3	+8.5	+8.0	+6.8	+5.9	+4.8
No. of injections	12	12	6	5.6	12	12	6.9	7.7	4.6

significant difference was maintained throughout the second year; in which the prior PDT group (n =16) received a mean of 5.5 injections and the treatment naive group received a mean of 2.8 injections (P =0.014). The mean time interval from the previous PDT till first IVB injection was 5.27 ± 3.70mo. Pretreatment characteristics had no statistically significant difference between treatment naive and prior PDT groups. Multiple linear regression analysis was performed with all baseline factors: age, gender, CNV size, CNV lesion subtypes, duration of CNV, previous PDT treatment and baseline CFT had no association with change in BCVA at 12mo. Only baseline visual acuity was a significant predictor of mean BCVA change at 12mo (regression coefficient B = 1.68, P =0.015) and at 24mo (regression coefficient B = 0.705, P =0.024) in regression model.

DISCUSSION
The perceived clinical similarities to ranibizumab and the much cheaper cost of bevacizumab had led to its widespread use in ophthalmic patients even before data was available from clinical trials of head-to-head comparison between the two drugs. Comparison of AMD treatments trial was a two-year investigation that enrolled and randomized 1107 patients with CNV into four different treatment groups: ranibizumab or bevacizumab in a monthly or an as-needed regimen [3-4]. The study was performed without financial support from the pharmaceutical industry, a rarity for prospective trials of this size. At 12mo, bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 ETDRS letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 ETDRS letters gained respectively [3]. Our study obtained a mean gain of 4.76 letters at 12mo. The proportion of patients who gained >15 letters was 33.3%, which was similar to the results from randomized control trials (RCTs) (Table 2). However, the proportion of patients who did not have a decrease in visual acuity of 15 letters or more from baseline was slightly lower (90.1%) in our series when compared with the cohorts in clinical trials (Table 2). Similar to the CATT study, most of the change in mean visual acuity occurred during the first year, with relative little change during the second year[4]. Nonetheless, for patients that completed 24mo of follow-up in this study, 27.3% of eyes gained >15 letters

and 81.8% lost <15 letters.

One of the potential reasons for less optimal visual outcome in our study compared with clinical trials is the lower mean number of injections (4.6 vs 7.7 in CATT year 1, and 9.2 vs 14.1 in CATT year 2). Such discrepancy in visual outcome of IVB treatment in routine clinical practice was attributed to poorer compliance to treatment protocol, longer time intervals between follow-up visits, less number of follow-up OCTs performed and fewer reinjections [10-16]. The Swedish Lucentis Quality Registry found a good improvement in visual acuity after 3 injections of ranibizumab, but this subsequently dropped back to pretreatment levels [13]. Similar results were found by the WAVE study in Germany and in the French Lumiere study [10,14-15]. Nonetheless, in a multi-center prospective audit of 12mo outcomes of anti-VEGF for 1140 treatment-naïve AMD patients in Australia that received a higher mean number of injections (7 injections) than previous observational studies, the reported improvement was 4.7 logMAR letters, which was still somewhat less than the visual gain in phase 3 clinical trials[16]. Besides the number of injections, case selection, methods in visual acuity measurement [using Snellen charts, early treatment diabetic retinopathy study (ETDRS) charts or electronic visual-acuity tests], OCT parameters in monitoring disease activity and treatment regimens also contributed to the differences in visual outcomes in observational studies compared with clinical trials.

Our study observed that the greatest increase in visual acuity in the subgroup of patients with baseline visual acuity <20/320 and patients with poorer visual acuity were not recruited in clinical trials. Furthermore, our study revealed that the only statistically significant covariate that influenced visual outcome identified by regression analysis in our study was baseline BCVA. The MARINA and ANCHOR subgroup analyses recognized that the most important predictors of visual acuity outcomes were baseline visual acuity, followed by CNV lesion size and age [17-18]. It implied that patients with lower baseline visual acuity probably had a greater chance for improvement from baseline over time (ceiling effect), and vice versa (floor effect) for those with higher baseline visual acuity (floor effect). Baseline predictors for 1y visual outcome identified in CATT study were age, CNV lesion size, and elevation of retinal pigment epithelium [19]. These

predictors did not vary by treatment group (ranibizumab *vs* bevacizumab, monthly *vs* as-needed injections). Our study did not find a statistically significant association between CNV lesion size and age in our series, possibly because the sample size was not large enough and associations between age and CNV lesion size with visual outcome were weak. Nevertheless, our study has shown that bevacizumab is efficacious in neovascular AMD patients whose baseline visual acuity is below those who were recruited in RCTs.

Subgroup analysis in our study revealed no statistically significant difference in baseline characteristics and visual outcomes at 12, 24mo between treatment naïve and prior PDT patients. Carneiro *et al* [20] also reported that bevacizumab was effective in improving visual acuity without a statistically significant difference between the two groups. Jyothi *et al* [21] reported 2 cases of RPE rip at the extrafoveal edge of fibrotic lesion after anti-VEGF injections in their series of 25 prior PDT-treated eyes. None of the subjects had increased RPE atrophy and the majority had improved or stabilized vision (loss of <15 ETDRS letters) at 6mo. Patients who had prior PDT in our series required significantly more mean number of injections per year than treatment naive patients at 12mo, possibly because these patients were more prone to recurrence or persistence of CNV. In theory, prior PDT may increase retinal and subretinal fibrosis and induce choriocapillary atrophy which could limit the potential visual recovery of patients subjected to anti-VEGF [22]. Nevertheless, in clinical practice, patients who had reactivated or persistent CNV after PDT could still benefit from IVB because the two therapies may have different mechanisms in treating neovascular AMD[23].

No significant vision threatening ocular side effects, such as endophthalmitis and retinal detachment, occurred in this series during the entire period of follow-up. Nonetheless, the sample size in our series may be too small to detect ocular adverse events following IVB. McCannel [24] reported the incidence of endophthalmitis was 0.049% (approximately 1 of 1949 injections) in a meta-analysis of 105 531 injections from all major U.S.-based studies from 2005-2010. Arevalo *et al* [25] reported no systemic adverse events in the group of neovascular AMD patients that received 1.25 mg, but for the group that received 2.50 mg, the incidences of systemic adverse events was higher (2.6% had arterial hypertension and 1.3% had stroke). No systemic adverse event occurred in our series in which the majority received 1.25 mg bevacizumab and only 5 patients received 2.50 mg.

There were no differences in endophthalmitis rates or mortality between treatment groups in the CATT study, however, more patients that received bevacizumab had multiple systemic serious adverse events than those receiving ranibizumab, 24% *vs* 19% at 1y and 40% *vs* 32% at 2y[3-4].

Nonetheless, these adverse events were distributed across a wide range of organ class, and many seemed unrelated to VEGF suppression. These adverse events included infections, palpitations and accidents. In the inhibition of VEGF in age-related choroidal neovascularization (IVAN) trial, a United Kingdom-based study involving 610 patients comparing bevacizumab with ranibizumab, given either monthly or as needed, there were more arteriothrombotic events and heart failure with ranibizumab [26-27]. It has been argued that sample sizes of CATT and IVAN trials were insufficiently powered to identify differences in drug-related adverse events. The variable rates of adverse events amongst studied subjects, and even amongst controls, may suggest type I error[28].

The hypothesis that the greater binding affinity of aflibercept may equate to a clinically higher efficacy and/or longer duration of action compared to ranibizumab was tested in two phase-III non-inferiority studies, VIEW 1 and VIEW 2[5]. It was demonstrated that both aflibercept monthly and aflibercept every two months after three initial monthly doses groups were non-inferior to monthly ranibizumab in terms of the amount of vision gained. Clinically, this may give patients and physicians another therapeutic option that involves injection every two months after three loading monthly doses, which could reduce the risk associated with regular intravitreal injections and the treatment burden to patients. In a trade-off analysis of efficacy and adverse events of aflibercept, ranibizumab and bevacizumab in AMD patients, bevacizumab has some disadvantages in severe side effects compared with the other two licensed drugs, whereas the efficacy and side effect profiles of ranibizumab and aflibercept were very similar[29].

Although many factors determine the choice of anti-VEGF drugs for the treatment of AMD, their significant difference in cost has been an important factor. The single-dose cost of aflibercept (US $1850) is comparable to ranibizumab (US $1950), but still substantially more than bevacizumab (approximately US $50)[29-32]. Since the single-dose costs and efficacies of the two drugs are comparable, physicians' use of aflibercept instead of ranibizumab may largely depend upon their perceptions of the drugs' durability. The cost of treating patients with aflibercept 2 mg every 8wk may be approximately half that with ranibizumab. Cost-conscious physicians, however, will also be forced to consider the relative merits of more expensive, less frequent dosing with aflibercept versus the more frequently dosed, lower cost alternative, off-label bevacizumab. Given the rising demands for healthcare and limited budgets, local evidence on incremental cost and cost-effectiveness is of particular importance in deciding the treatment of choice in AMD patients.

Our study was limited by small sample size. A larger sample size would have allowed for more power to analyze differences across subgroups. The study evaluated patients who returned for follow-up appointments, but patients who did poorly or exceptionally well may have defaulted follow-up visits. Furthermore, there was no standardized criteria for retreatment. We have converted Snellen acuities to logMAR letters in an attempt to standardize our results with published clinical trials for comparison; however, this may not match exactly with ETDRS visual acuities [33-34]. There were two different dosages of bevacizumab in this study. Considering the fact that ranibizumab has a molecular weight approximately one third of bevacizumab, the dose of bevacizumab containing the same number of molecules would be approximately 1.25 mg [35]. Some physicians believed that increasing the dosage to 2.50 mg could improve its efficacy. However, a head-to-head trial revealed no difference in effect between the two dosages[35].

The significance of data from observational studies is that they provide an indication of what is happening in routine clinical practice, in contrast to results of tightly controlled clinical trials, which may or may not be achievable in routine practice. Our study can be useful in providing patients' expectations for visual stabilization or improvement after receiving less-than-monthly IVB, which may be a more preferable treatment regimen especially when cost is a concern. More frequent follow-up visits and OCT assessments of disease activity may optimize efficacy in clinical practice. Furthermore, our study had revealed that bevacizumab may be safe and efficacious in neovascular AMD patients who received prior PDT and in those with baseline BCVA <20/320, while no evidence had been provided by RCTs on these subgroups.

ACKNOWLEDGEMENTS

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