

# Clinical research on intravitreal injection of bevacizumab in the treatment of macula lutea and retinal edema of ocular fundus disease

Ying Yan<sup>#1</sup>, Tao Wang<sup>#1</sup>, Jing Cao<sup>2</sup>, Meng Wang<sup>1</sup> and Fenghua Li<sup>1\*</sup>

<sup>1</sup>Ophthalmology, Linyi People's Hospital, Shandong, China

<sup>2</sup>Department of pharmacy, Linyi People's Hospital, Shandong, China

**Abstract:** This paper aimed to explore clinically curative effect of intravitreal injection of bevacizumab in the treatment of macula lutea and retinal edema of ocular fundus disease. The number of 300 patients (390 eyes) with ocular fundus diseases including retinal vein occlusion (RVO), diabetic retinopathy (DR), age-related macular degeneration (ARMD), central serous chorioretinopathy (CSC), choroidal new vessel (CNV) received and cured in the hospital from February 2010 to February 2014 were given intravitreal injection of bevacizumab (1.5mg) with once per month and a total of 2-3 times. Results of patients' vision and fluorescence fundus angiography (FFA), optical coherence tomography (OCT) before and after treatment were compared and curative effects were evaluated. Vision of 349 eyes (89.49%) improved obviously with the average of more than 2 lines, patient's intraocular pressure (IOP) was normal and all indexes were clearly better; vision of 26 eyes (6.67%) was stable before the treatment and without any changes after the treatment, the situation of fundus got better without increased IOP; vision of 15 eyes (3.85%) decreased to some extent, and the symptoms eased slightly after symptomatic treatment. In the 1st day after intravitreal injection, best-corrected visual acuity increased to  $0.239\pm 0.175$ , best-corrected visual acuity in 1 m was  $0.315\pm 0.182$ , in 3m continuously climbed to  $0.350\pm 0.270$ , and in 6 m was  $0.362\pm 0.282$ . Compared with vision before injection, t value was  $t=3.184$ ,  $t=7.213$ ,  $t=9.274$  and  $t=9.970$  ( $P=0.002$ ,  $P=0.000$ ,  $P=0.000$  and  $P=0.000$ ) respectively, and all P were less than 0.01. Furthermore, the difference was significant if  $\alpha=0.01$ , which could confirm that 1m best corrected visual acuity of patients after intravitreal injection improved clearly in combination with before injection and 3m and 6 m visions enhanced constantly after injection. To sum up, intravitreal injection of bevacizumab in treating ocular fundus disease improves patient's vision effectively, also relieves macula lutea, retinal edema and other symptoms obviously, and promotes the hemorrhage absorption of vitreous body and retina.

**Keywords:** Vitreous body; Bevacizumab; Ocular fundus disease.

## INTRODUCTION

In ocular fundus diseases, retinal vein occlusion (RVO), diabetic retinopathy (DR), age-related macular degeneration (ARMD), central serous chorioretinopathy (CSC), and choroidal new vessel (CNV) influence patient's vision most with long therapeutic process and easy recurrence (Mathias *et al.*, 2009), and conventional treatment will burden patients physically and psychologically.

Bevacizumab has good effect on treating retinal vascular disease, but it is only approved for the treatment of colorectal cancer; bevacizumab is external drug for treating AMD indications. In Shanghai "eye medicine" event in 2010, 61 patients infected endophthalmitis using intravitreal injection of bevacizumab for treating eye diseases in Shanghai First Peoples Hospital. Researches on bevacizumab in the treatment of ophthalmic diseases reduced sharply after this event (Xi, 2010).

In 2006, ranibizumab was approved for treating neovascular eye diseases. To date, it has been brought into health insurance in the United States. But this drug cannot

be popularized effectively in our country due to its high price and limited economic development level.

Bevacizumab as a drug having similar effect to ranibizumab has relatively low price. Based on this, we conducted this experiment in view of curative effect and security of bevacizumab in the treatment of exudative AMD.

## MATERIALS AND METHODS

### General materials

A total of 300 patients (390 eyes) with ocular fundus disease (with one week to seven years disease course) received and cured in our hospital from February 2010 to February 2014 were selected, in which, 158 cases (a total of 210 eyes) were male (53.85%) with age ranged from 23 to 73 years (mean 45.3 years); 94 cases (97 eyes) were confirmed as RVO (24.87%); 64 cases (113 eyes) were DR and all in or above III stage (28.97%); 45 cases (68 eyes) were ARM (17.44%) including 30 wet cases (45 eyes) and 15 dry cases (23 eyes); 60 cases (53 eyes) were CSC (13.59%); 37 cases (59 eyes) were CNV (15.13%).

\*Corresponding author: e-mail: lfh@ibhsedu.com

# these authors contributed equally to this study and share first authorship

Before the treatment: 20 eyes had over 0.5 vision (5.13%); 49 eyes had over 0.3 vision (12.56%); 152 eyes had over 0.1 vision (38.97%); 157 eyes had vision between 0.1 and 0.01 (40.26%), 12 eyes had less than 0.01 vision (3.08%); and the average IOP was (17.60±2.30) mmHg. This experiment was approved by ethics committee of this hospital and all patients signed informed consent.

**Inclusion and exclusion criteria**

Referring to fundi disease group in ophthalmology branch of Chinese medical association (CMA), fundus macular and retinal edema were diagnosed in clinic, patients who conformed to following standards were included in research group: 1) patients were diagnosed as fundus macular and retinal edema; 2) patients had history of vision or metamorphosis; 3) pigment disorder and pigment loss existed in macular region in binocular indirect ophthalmoscope examination; 4) decipherable fundus fluorescein angiography (FFA) image was available, and patients were proved to be in the initial treatment by regular test; 5) qualified optical coherence tomography (OCT) image was available. Exclusion standards contained: 1) dioptric media including severe keratopathy, cataract and vitreous hemorrhage were turbid, which influenced treatment and detection; 2) patients were allergic to fluorescent contrast agents; 3) patients received photon dynamic treatment (PDT) or transpupillary thermotherapy (TTT) treatment; 4) patients had blood coagulation disorder or were using anticoagulant drugs except aspirin; 5) patients were with uncontrollable hypertension, active infection, etc.

**Method**

Two hours before the treatment, patient’s local eyes were treated by dropping antibiotics eye drops. After conjunctiva sac was washed by conjunctiva sac with 0.9% sodium chloride injection (adding with 16 U gentamicin per 500mL), 5g/L oxybuprocaine hydrochloride eye drops (Zhengqin Pharmaceutical Group Co., LTD, Hunan; specification: 5mL: 25mg, approved number: H43021020) was dripped into eyes. In a sterile environment, surgical needles were vertically stabbed into the vitreous body in flat part of ciliary body 4mm behind limbus corneae when operating, then 1.5mg bevacizumab (trade name: Avastin; Roche Pharma Schweiz Ltd., Germany; specification: 400mg: 16mL; imported drug registration number: S20120069) was injected immediately, once a month, for a total of 2-3 times. Before bandaging, Tobradex eye ointment containing 0.3% tobramycin, 0.1% dexamethasone (s. a. ALCON-COUVREUR n. V., Belgium; imported drug registration number: H20080660) was used for smearing conjunctiva sac, and then the eyes were bandaged with sterilized dressing block. To reduce exudation and leakage of bevacizumab and intensify detumescence, patients besides CSC patients were given triamcinolone acetonide cream (approved number: H23023698; specification: 10g:

2.5mg). After the operation, they were reviewed periodically and examined by ophthalmoscopy, FFA, OCT in order to observe bleeding absorption, new vessels fade, macular edema fade.

**STATISTICAL ANALYSIS**

SPSS 19.0 statistical software was used for analysis, and measurement data was expressed by mean ± SD. Statistical processing between group and multiple inter-group were performed with t test and analysis of variance (ANOVA), and the difference had statistical significance if P<0.05.

**RESULTS**

Patients were reviewed periodically and examined by ophthalmoscopy, FFA, OCT in order to observe bleeding absorption, new vessels fade and macular edema fade.

**Changes of vision and IOP value before and after intravitreal injection of bevacizumab in the treatment of exudative macular degeneration**

Results of changes in vision and IOP value before and after intravitreal injection of bevacizumab in the treatment of exudative macular degeneration are shown in table 1 and table 2 respectively.

**Table 1:** Changes of vision before and after intravitreal injection of bevacizumab

Time Points	Mean ± SD	t	P
Baseline	0.195±0.181		
1d	0.239±0.175	3.184	0.002
1m	0.315±0.182	7.213	0.000
3m	0.350±0.270	9.274	0.000
6m	0.362±0.282	9.970	0.000

**Table 2:** Changes of IOP value before and after intravitreal injection of bevacizumab

Time Points	Mean ± SD	t	P
Baseline	15.1±2.26		
1m	15.3±2.71	0.821	0.718
3m	14.9±2.30	0.844	0.691
6m	15.2±2.28	0.813	0.935

**Curative effect analysis of all kinds of ocular fundus diseases**

After treatment, 349 eyes of patients (89.49%) were featured by significantly improved vision, normal IOP, vanished retinal edema, obviously absorbed bleeding, faded new vessels and markedly enhanced OCT and FFA index. A total of 26 eyes (6.67%) were characterized by stable vision before and after treatment, unobvious changes after the treatment, enhanced eye ground and without improved IOP or new vessel growth. Vision of 15 eyes (3.85%) decreased to some extent, in which, one eye occurred endophthalmitis two days after operation, and

vision decreased from 0.5 to 0.1; and two eyes had rhegmatogenous retinal detachment (RRD) after operation. Vision of patients occurring complications improved somewhat after symptomatic treatment. Patient's best corrected visual acuity before and after treatment had statistical difference ( $P < 0.05$ ). Please refer to table 3.

## DISCUSSION

### *Relevant research on macula lutea and retinal edema of ocular fundus disease*

Plenty of domestic and international epidemiological data have confirmed that senility is one of the most dangerous factors for AMD. Although incidences in different age group obtained from various researchers are diverse, the overall trend is basically identical, that is to say, AMD onset risk increases significantly with age (Paulus T V M de J, 2006). In America, 1.47% people (over 40 years) suffer from wet AMD, and its incidence rate rises rapidly with age. People over 80 years increase to 19%, other 8 million people are characterized by rigid glass membrane wart and 7 million people showing soft glass membrane wart are extremely risky to become wet AMD. In addition, the number of American patients with wet AMD is expected to rise to 3 million by 2020 as population grows (The Eye Diseases Prevalence Research Group, 2004). Three large population-based studies (Beaver Dam Eye, Rotterdam and Blue Mountains Eye) verify that prevalence rate of AMD accounts for 1.2% in common people (55-64 years) while reaches up to 13% in people over 85 years. In the meantime, those three studies find that rigid glass membrane wart intergrades gradually, and accompanied with changes in pigmentation, which is the major performance that incidence rate of wet AMD increases gradually (Paul M et al., 2002; Redmer L et al., 2003).

Recently, influence of pharmacy history on AMD incidence has drawn much attention from researchers. A study shows that antacid, inhibin and anti-inflammatory agent can reduce onset risks of AMD, and whether gender becomes a dangerous element for AMD still remains dispute. After taking age as a continuous variable in regression model, it is found that gender has no significant correlation with AMD onset risk. Therefore, part of researchers summarize that results containing gender difference in AMD incidence are likely to be caused by race, environment, etc. and also selection bias of people who are surveyed. Study on AMD prevalence rate based on different races indicates that AMD

incidence rate of people from different nations, groups and geographic positions is various, and a majority of scholars still support the view of "race affects AMD" although this kind of difference may be caused by differences of genetic background or some other risky factors (Xiao L, 2010). Relationship between cataract and AMD incidence has no conclusion, but most scholars consider that cataract surgery is one of the dangerous factors leading to AMD. Some researches suggest that cataract surgery not only increases the threats of dry AMD on normal people, but also can result in condition involving into wet after dry AMD patients go through cataract surgery (Jiejun W et al., 2003). For a long time, a lot of researchers doubt that common pathogenic factors are possible to exist in cardiovascular and cerebrovascular diseases including atherosclerosis, thrombosis, myocardial infarction and stroke, as well as in AMD, because pathogenesises of both of them involve lipid deposition, inflammatory response, oxidative stress and other injuries. Furthermore, arteriosclerosis is able to thicken and harden choroid vascular wall, constrict inner diameter, increase blood flow resistance, reduce tissue blood supply, thus damaging RFE function and separating cone from rod acromere, and finally AMD is generated (Wong TY et al., 2007; Yinkang D et al., 2007).

### *Effects of intravitreal injection of bevacizumab in the treatment of macula lutea and retinal edema of ocular fundus disease*

Ocular fundus disease RVO, DR, CSC, ARMD and CNV featured by hard healing, long disease course and easy recurrence, affects patient's vision severely, or even leads to blindness, which brings about significant negative impacts to patients physiologically and psychologically (Xiaorui and Xuezhen, 2010). Etiological treatment and laser therapy are the main methods for treating ocular fundus disease, but the complications caused by traditional therapy is able to aggravate illness, i.e., macular oedema and proliferation of new vessels (Tong et al., 2009). Macular oedema is caused by permeability increase of vessels due to Blood-Retinal Barrier (BRB) damage, and liquid increase in macular region can induce cell fibrosis (Hao and Qinghuai, 2010). Proliferation of new vessels, a kind of more severe complication, gives rise to retinal ischemia and hypoxia, thereby resulting in edema and increasing IOP. Although complications can be treated by a lot of methods, they cannot be fundamentally cured. Intravitreal injection of bevacizumab, a new therapy treating ocular fundus disease, can effectively inhibit new vessels, reduce vessels leakage, relieve macula lutea, retinal edema and other complications (Li

**Table 3:** Curative effect analysis of all kinds of ocular fundus diseases [eye(%)]

Curative effect	RVO (n=97)	DR (n=113)	ARM (n=68)	CSC (n=53)	CNV (n=59)	Total (n=390)
Effective	88(90.72)	100(88.50)	61(89.71)	49(92.45)	51(86.44)	345(89.49)
Invalid	5(5.15)	7(6.19)	6(8.82)	3(5.66)	5(8.47)	26(6.67)
Worsen	4(4.12)	6(5.31)	1(1.47)	1(1.89)	3(5.08)	15(3.85)

and Guohua, 2012). Thus it was found that intravitreal injection of bevacizumab is a safe and rapid therapy treating ocular fundus disease, which is worth further study and popularization.

### Limitations

As a forward-looking and non-randomized clinical intervention study, this experiment has no control group, small sample size and short observation time, resulting in bias results. Therefore, clinical experiment with large sample and good matched cases-control study are needed to be performed from now on so as to evaluate curative effect of intravitreal injection of bevacizumab in treating macula lutea and retinal edema of ocular fundus disease objectively.

### CONCLUSION

Intravitreal injection of bevacizumab considered as preferred therapy treating exudative AMD can ease vessels leakage, reduce retinal thickness in macular region, and also improve patient's vision effectively. We discover that this therapy in treating new vascular disease of fundus is featured by good curative effect and less complications. Patients treated by intravitreal injection of bevacizumab are found with good tolerance, no systemic and ocular side effects and no big complications in ocular region. This method can improve patient's vision effectively and relieve macula lutea and retinal edema obviously, and promote absorption of bleeding in vitreous body and retina.

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