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Original Article

Intravitreal injections of ranibizumab in treatment of idiopathic choroidal neovascularization

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Abstract: Objectives: To evaluate the efficacy and safety of intravitreal injections of ranibizumab in early treatment of idiopathic choroidal neovascularization. Methods: Data of 30 patients diagnosed with idiopathic choroidal neovascularization at Jining No. 1 People's Hospital were retrospectively analyzed. All patients received intravitreal injections of ranibizumab. All patients returned for follow-up visits 2 weeks, 1 month and 3 month after their first intravitreal injection. Patients were divided into two groups according to disease duration, that is, ≤3 months (group A) and >3 months (group B), and the data were compared. Results: With the time, visual acuities of patients significantly increased after treatment. Visual acuities of group A were significantly higher than group B 2 weeks after treatment. Visual acuities of patients were no significant differences 1 month and 3 months after treatment between the two groups. No adverse effects were observed in this study. Conclusion: Intravitreal injection of ranibizumab was an effective and safe strategy to treat patients with idiopathic choroidal neovascularization. It worked faster in early idiopathic choroidal neovascularization.

Keywords: Intravitreal injection, ranibizumab, idiopathic choroidal neovascularization

Introduction

Seventeen percent of all cases of choroidal neovascularization (CNV) in patients less than 50 years of age are idiopathic [1]. Idiopathic choroidal neovascularization (ICNV) is defined as a CNV develops in the apparent absence of any coexistent ocular or systemic disease, typically in young patients without any signs of age-related macular degeneration [1-3]. This particular variant of ICNV is thought to have a relatively benign course [1, 3]. However, the natural course of the disease can be unpredictable because of significant individual variations [3, 4]. A summary of long-term results reported that 21% of untreated patients with idiopathic CNV showed a decrease of more than 0.2 in visual acuity [4, 5]. Severe, permanent, and irreversible loss of vision can occur in some eyes without treatment [1].

Among the treatment modalities for ICNV, photodynamic therapy (PDT) with verteporfin has once been recommended as a main method for the treatment of CNV. It can effectively and selectively occlude CNV without causing significant damage to the overlying neurosensory retina, but the results are rather inconsistent [6, 7]. It may also bring severe adverse effects, such as damage to the retinal pigment epithelium and choriocapillaries [8, 9] and reduce choroidal thickness in some diseased eyes [10, 11].

Intravitreal ranibizumab therapy has been accepted as a predominant treatment for CNV in recent years. Ranibizumab is a kind of anti-vascular endothelial growth factor (anti-VEGF) agents. Studies have proven the efficacy of intravitreal ranibizumab injection for CNV by showing favorable visual outcome and central retinal thickness (CRT) reduction after the treatment [12, 13]. A comparative study looked at intravitreal ranibizumab (IVR) versus PDT and found IVR superior to PDT in terms of visual gain and its maintenance. Other studies have also reported promising results with ranibizumab in young patients, with timing of the injection (early vs. midterm presentation) as an important prognostic factor [14, 15]. Fan et al [14]

Table 1. Clinical characteristics of patients with idiopathic choroidal neovascularization

	Group A (n=16)	Group B (n=14)	Total (n=30)
Sex (male/female)	7/9	9/5	16/14
Age (year)	28.50±5.03	30.21±6.05	29.30±5.50
Age of onset (year)	27.69±4.87	29.29±6.21	28.43±5.49
Duration of disease (month)	2.50±0.63	6.57±3.30**	4.40±3.06
Central macular thickness (μm)	464.81±76.77	512.29±73.02	486.97±77.58
Visual acuity			
Before treatment	0.21±0.15	0.13±0.06	0.17±0.12
2 weeks after treatment	0.42±0.19	0.27±0.11*	0.35±0.17
1 month after treatment	0.54±0.15	0.44±0.16	0.49±0.16
3 months after treatment	0.55±0.10	0.46±0.16	0.50±0.14

*P<0.05 *vs.* Group A; **P<0.01 *vs.* Group A.

defined early intervention as therapy administered to patients with less than 3 months of disease duration, whereas midintervention was defined as therapy administered within 3 to 6 months of disease duration. However, the results about the influence of ranibizumab therapy on choroid in the treatments of age-related macular degregation (AMD), polypoidal choroidal vasculopathy (PCV), and CNV with myopia were reported differently [16, 17]. And there is not many study of ranibizumab therapy in the treatment for ICNV.

In this study, we evaluated the efficacy and safety of intravitreal injections of ranibizumab in early treatment of ICNV.

Methods

Patients

From January 2007 to December 2014, 30 patients were diagnosed with ICNV in one eye. All patients underwent a visual examination based on the early treatment diabetic retinopathy study (ETDRS) eye chart, indirect ophthalmoscopy, fundus fluorescein angiography (FFA), optical coherence tomography (OCT). We have obtained informed consent of these patients. The patients of this study were treated according to the World Medical Association Declaration of Helsinki ethical principles and the study was approved by the Ethics Committee of Jining No. 1 People's Hospital.

The patients included in the study met the following criteria: 1) patients <50 years old; 2) absence of concurrent ocular diseases in the study eyes that compromised or could have compromised vision and ocular conditions; 3) no signs of pathologic myopia, including chorioretinal atrophy, posterior staphyloma, and lacquer cracks at the time of diagnosis; 4) evidence of macular CNV lesions and leakage on FFA examination.

The exclusion criteria were 1) history of prior treatment for CNV, including laser, submacular surgery, or radiation; 2) history of a sub-Tenon capsule injection of triamcinolone acetonide, photodynamic laser treatment (PDT), or anti-VEGF injection in the 6months before the baseline treatment of idiopathic CNV; 3) cataract surgery during follow-up; 4) significant hepatic disease such as active hepatitis, hypersensitivity, or allergy to fluorescein (excluded because of the absence of angiographic studies) [13].

Patients were divided into two groups according to disease duration, that is, ≤3 months (group A) and >3 months (group B).

Treatment

All injections were performed in the operating room with a sharp 29-gauge needle. The needle was inserted into the eye through the pars plana, 3.5-4 mm from the limbus. Ranibizumab 10 mg/mL (Genentech, Inc., 0.5 mg in 0.05 mL) was intravitreally injected. All patients returned for follow-up visits 2 weeks, 1 month and 3 month after their first intravitreal injection.

Eyes were retreated when any of the following conditions occurred: 1) a visual acuity loss more than 0.1 or unconsciously decreased vision; 2) the presence of subretinal fluid on OCT examination; 3) new bleeding macular lesions; 4) increases in CNV lesion leakage or new lesions on FFA examination.

Statistical analysis

SPSS 18.0 was used for statistical analysis. Numerical data were expressed as mean ±

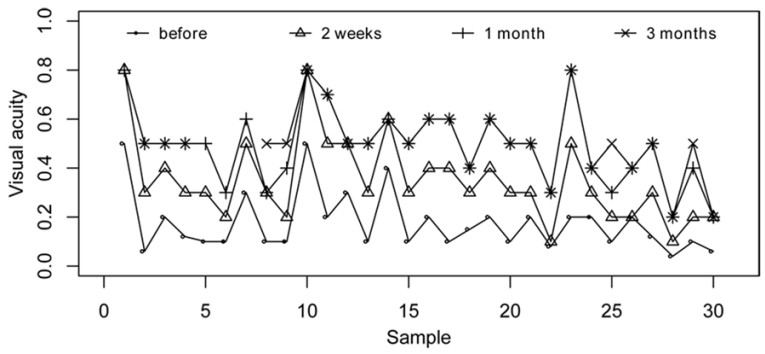

Figure 1. Visual acuity of each patient before treatment, 2 weeks, 1 month and 3 months after treatment.

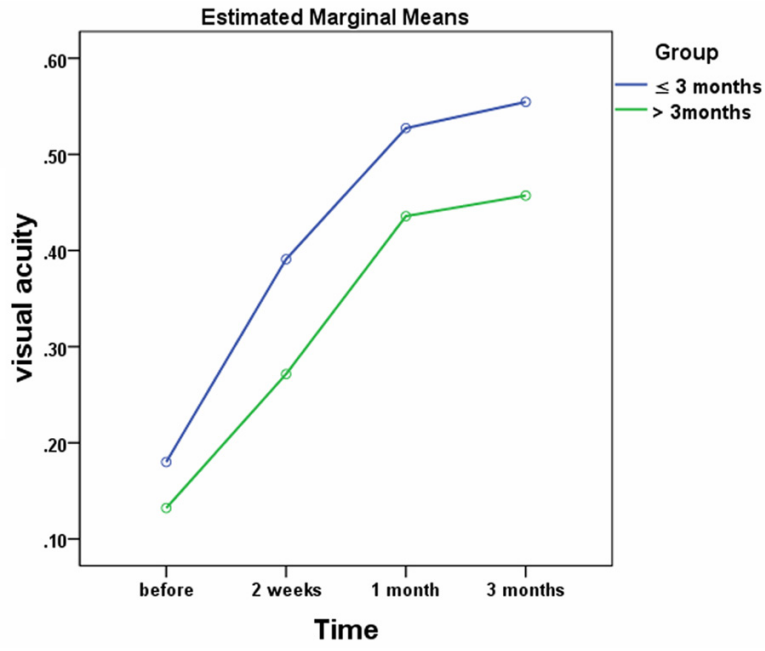

Figure 2. Visual acuities of patients in two groups before and after treatment were analyzed by repeated measures ANOVA.

standard deviation (SD) ($\bar{x}\pm s$). Visual acuity before and after treatment were compared using repeated measures ANOVA. The two groups were compared using *t* test. A chi-squared test was used to compare values between the groups. $P<0.05$ indicated a significant difference.

Results

Baseline characteristics of patients

A total of 30 patients were enrolled in this study. Among them were 16 men (16 eyes) and 14 women (14 eyes). The patients were aged 21-41 years with a mean age of 29.30±5.50 years and mean an disease duration of 4.40±3.06 months. There were no significant differences between the two groups in gender, age, age of onset, central macular thickness and visual acuity before treatment (**Table 1**).

Intravitreal injections of ranibizumab was effective and safe for patients with ICNV

Visual acuity of each patient significantly increased after treatment (**Figure 1**). Time was an influence factor for the treatment effects ($P<0.01$), however grouping did not affect the prognosis in the repeated measures ANOVA (**Figure 2**). It indicated that intravitreal injection of ranibizumab was effective for patients with ICNV, however disease duration did not affect treatment effects.

Not any adverse reactions were observed in patients in this study. It suggested that intravitreal injection of ranibizumab was safe for patients with ICNV.

Intravitreal injections of ranibizumab worked faster in early ICNV

Visual acuities of group A were significantly higher than group B 2 weeks after treatment. Visual acuities of patients were no significant differences 1 month and 3 months after treatment between the two groups. Although disease duration was not an influence factor of treatment effects, it seemed that intravitreal injections of ranibizumab worked faster in patients with early ICNV (disease duration ≤3 months).

Discussion

CNV is a progress regulated by multiple cytokines, among them vascular endothelial growth

factor (VEGF) is major one. VEGF is a cytokine with highly selectivity to endothelial cells. VEGF induces the expression of urokinase and tissue plasminogen activators and expression of matrix metalloproteinase and collagenase, promoting the degradation of extracellular matrix, facilitating the migration of vascular endothelial cells [18]. Binding with its receptor, VEGF accelerates the mitosis and growth of vascular endothelial cells, increasing vascular endothelial cells and vascular permeability [19]. That provides a theoretical basis for anti-VEGF treatment for CNV.

ICNV is characteristic as isolated CNV in macular region with unknown causes, repeated bleeding out, cicatrization, and patients with seriously decreased vision and irreversible loss of vision [20]. Studies suggested that levels of angiogenesis factors in body were associated with pathogenesis of ICNV, and expression of VEGF in patients with ICNV significantly increased [21, 22]. Without etiological treatment, anti-VEGF was an effective treatment method for patients with ICNV.

Ranibizumab (Lucentis), is a monoclonal antibody approved by Food and Drugs Administration (FDA) in 2006 for the treatment of wet AMD. Ranibizumab can bind with all subtypes of VEGF-A, inhibiting the binding of VEGF and VEGF receptor expressed on the surface of the vascular endothelial cells, so that prevents the neovascularization, reduces capillary leak, and relieves tissue edema, to treat CNV [23, 24]. Ranibizumab inhibited the proliferation and migration of human umbilical vein endothelial cells (HUVEC) and retinal pigment epithelium (RPE) in a concentration-dependent manner. Mordenti et al's study indicated that ranibizumab injected in vitreous of monkey fully penetrated the full thickness of retina within 1 hour and had a half-life of 3.2 days in vitreous. Compared with intravenous injections and subconjunctival injections, intravitreal injections of ranibizumab were the best method of administration. Ranibizumab injected reaching a highest concentration in vitreous could reduce the adverse reactions induced by abnormal VEGF in other parts of the body. In Hamoudi et al's study, 12 patients with CVN were given 3 consecutive intravenous injections of 0.5 mg ranibizumab every 4 to 6 weeks, and visual acuities of all patients were improved at the end of the follow-up. It indicated that intravenous injections of ranibizumab were effective for patients with CNV. In our study, visual acuities of all patients with ICNV were improved. And visual acuities of group A were significantly higher than group B after the 2-week treatment. It indicated intravenous injections of ranibizumab work faster in early stage of the disease. It might because that there were more reversible components in the early stage of ICNV which was a progress including bleeding out, edema, exudation, cicatrization and fibration.

Due to the relatively short half-life of ranibizumab in vitreous, it usually needed repeated injections in treatment for patients with AMD [25, 26]. In our study, only one male patient in group A received the second injection treatment in the 3-month follow-up. However, in this study we only observe the short-term treatment, so that a long-term study would be needed in the further study.

Intravenous injections of ranibizumab were proved safe without any toxic effects of retina by a large amount of animal and clinical experiments [27]. Adverse effects reported previously included intraocular pressure elevation, ophthalmecchymosis, retinal vascular occlusion and et al. Nevertheless there were not any adverse reactions observed in patients in our study. Since the sample size was small in this study, a large number of patients from multiple centers should be collected to study the possible adverse effects of intravenous injections of ranibizumab for patients with ICNV.

In conclusion, intravitreal injection of ranibizumab was an effective and safe strategy to treat patients with ICNV. It seemed work faster in early idiopathic choroidal neovascularization.

Disclosure of conflict of interest

None.

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