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Original Article

Ranibizumab as needed therapy for wet age-related macular degeneration combined with serous pigment epithelial detachment

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Abstract: Purpose: To evaluate the effect of ranibizumab on wet age-related macular degeneration (wAMD) combined with serous pigment epithelium detachment (PED). Design: Retrospective, noncomparative case series. Methods: Thirteen eyes of 13 patients with wAMD and associated serious PED were included in the study. All the patients were treated with intravitreal ranibizumab as needed from the first injection and followed up for 12 months. The follow-up data included the best-corrected ETDRS letter score, maximum PED height, PED area and PED volume, and central retinal thickness (CRT) on ocular coherence tomography (OCT). Results: The mean ETDRS letter score was 57.54 ± 10.28 at the last visit compared to 46.69 ± 11.58 at the baseline ($t = -3.47$, $P < 0.05$). The mean change of the ETDRS letter score was 10.85 ± 10.84. The mean maximum PED height, area and volume at the baseline and month 12 were 342.38 ± 176.39 μm and 189.23 ± 134.69 μm ($z = -2.83$, $P < 0.05$), 5.12 ± 4.69 mm^2 and 2.74 ± 2.89 mm^2 ($z = -2.67$, $P < 0.05$), 1.07 ± 1.73 mm^3 and 0.25 ± 0.46 mm^3 ($z = -2.90$, $P < 0.05$), respectively. The CRT were decreased from 331.54 ± 60.08 μm at the baseline to 286.85 ± 82.47 μm at month 12 ($t = 1.85$, $P > 0.05$). The mean number of injections during the study period was 3.3 ± 1.1. Conclusions: Intravitreal ranibizumab as needed for treatment of wAMD combined with sPED was shown to be effective.

Keywords: Anti-VEGF, ranibizumab, wAMD

Introduction

Age-related macular degeneration (AMD) has become the major cause of severe vision loss in elderly adults in China [1, 2], which represents a challenge that will become more serious in the future because of the aging population. Pigment epithelial detachment (PED) is an important feature of wet AMD (wAMD), which is a separation of the retinal pigment epithelium (RPE) from the underlying Bruch membrane. PED may have many manifestations that can be classified to four categories according to FFA: drusen type, serous type, fiber exudative type and hemorrhagic type [3]. The existence of PED, regardless of the type, represents a poor visual prognosis [4-7]. And serous PED is the most common type, which is characterized by a smooth elevation of the RPE, with early uniform hyperfluorescence on angiography that remains bright, with sharp borders during the later phase of the angiogram [8]. Recently because anti-vascular endothelial growth factor (VEGF) agents have been used for wAMD [9], it has been reported that anti-VEGF therapy for PED might achieve an effective outcome [10-13]. But most treatments in the above studies were pro re nata (PRN) therapy after 3 consecutive monthly injections. And in China, Ranibizumab is not covered by insurance but is the only anti-VEGF agent available; so this retrospective study aimed to evaluate the efficacy of intravitreal ranibizumab as needed therapy for serous PED related to wAMD.

Materials and methods

Patients

This study is a retrospective, noncomparative case series. Between July 2012 and May 2013, 13 eyes of 13 patients with wAMD and associated serous PED were included in the study. All the patients were treated with intravitreal

Table 1. Baseline Characteristics of All Study Eyes

Injected eye, n	13
Right, n (%)	8 (61.5)
Left, n (%)	5 (38.5)
Number of patients	13
Male, n (%)	7 (53.8)
Female, n (%)	6 (46.2)
Age (year), mean ± SD (range)	69.2±7.58 (56-78)
ETDRS visual acuity, mean ± SD	46.7±11.6
PED height (um), mean ± SD	342.4±176.4
PED area (mm^2), mean ± SD	5.12±4.69
PED volume (mm^3), mean ± SD	1.07±1.73
CRT (um), mean ± SD	331.5±60.1

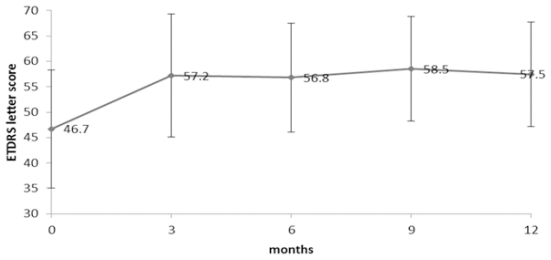

Figure 1. Change of visual acuity.

ranibizumab (Lucentis, Novartis, Stein, Switzerland) as needed from the first injection in Shanghai Tenth People's Hospital, Tongji University School of Medicine, and followed up for 12 months. The study was conducted according to the principles of the Declaration of Helsinki and informed consent was obtained from all the patients after the purpose of the study had been explained to them. The study was approved by the ethics committee of Shanghai Tenth People's Hospital.

The inclusion criteria were the presence of serous PED characterized by any evidence of the following: a sub-retinal hemorrhage; speckled hyperfluorescence on FA, consistent with occult CNV; sub-retinal fluid, or intra-retinal cysts on the OCT findings; best corrected visual acuity (BCVA) of 35-73 letters; and a maximum PED height of at least 150 μm. Patients with vascular PED were excluded from this study. Additionally, patients who had previous AMD treatment and other eye diseases potentially influencing the visual acuity were excluded.

The patients were evaluated at baseline and after the first injection at the monthly follow-up. At baseline, synchronous fluorescein angiography (FA) and indocyanine green angiography (IC-GA) were performed. The follow-up data included the best-corrected ETDRS letter score, maximum PED height, PED area, PED volume and central retinal thickness (CRT) on ocular coherence tomography (OCT) as well as the presence of relevant ocular complications. All the patients were scanned with a Cirrus OCT 4000 system (Carl Zeiss, Dublin, Ireland) using the macular thickness protocol, advanced RPE analysis protocol and 6-mm horizontal and vertical line scans. The PED height was measured manually on the OCT monitor using the built-in manual caliper tool.

Treatment

All the patients received 0.5 mg/0.05 mL ranibizumab injections via a 30-guage needle through the pars plana at the first injection. The injections were repeated for the occurrence of new or persistent sub-retinal fluid, retinal cysts, thickening, and enlarging PED according to OCT scan.

Statistical analysis

The statistical analysis was performed using SPSS 19.0 (SPSS for Windows 7, SPSS, Inc., IBM). The visual acuity and CRT changes were calculated with the Student's *t*-test. The PED height, area and volume changes were calculated with the Wilcoxon test. Spearman's test was used for the calculation of the correlations. The level of significance was set at $P < 0.05$ for all the statistical tests.

Results

Baseline characteristics

A total of 13 eyes of 13 Chinese patients (7 males, average age 69.2 years) met the inclusion criteria. The baseline characteristics are shown in **Table 1**.

Visual acuity outcome

The mean ETDRS letter score was 57.54 ± 10.28 at the last visit compared to 46.69 ± 11.58 at the baseline ($t = -3.47$, $P < 0.05$). The mean change of the ETDRS letter score was 10.85 ± 10.84. After 1 year, 13/13 (100%) eyes avoided moderate visual loss, 10/13 (76.92%) eyes had an increase in BCVA and 6/13 (46.15%) eyes had a gain of 15 or more on the ETDRS letter score. The mean ETDRS letter scores at 3, 6, and 9 months after the

Table 2. Statistical analysis of mean visual acuity, PED height, area, volume and CRT

	Baseline	3 mo	6 mo	9 mo	12 mo
BCVA					
SD	46.69±11.58	57.15±12.13	56.85±10.74	58.46±10.29	57.54±10.28
P value*		0.003	0.006	0.005	0.005
PED height (um)					
SD	342.38±176.39	211.92±117.28	203.85±151.16	207.31±176.41	189.23±134.69
P value*		0.01	0.01	0.02	0.01
PED area (mm^2)					
SD	5.12±4.69	3.02±3.82	2.92±3.07	2.82±3.03	2.74±2.89
P value*		0.002	0.005	0.006	0.008
PED volume (mm^3)					
SD	1.07±1.73	0.5±1.12	0.27±0.46	0.26±0.51	0.25±0.46
P value*		0.002	0.002	0.004	0.004
CRT (UM)					
SD	331.54±60.08	245.15±69.99	280.31±86.81	279.15±74.84	286.85±82.47
P value*		0.001	0.037	0.056	0.089

*Compared to the baseline.

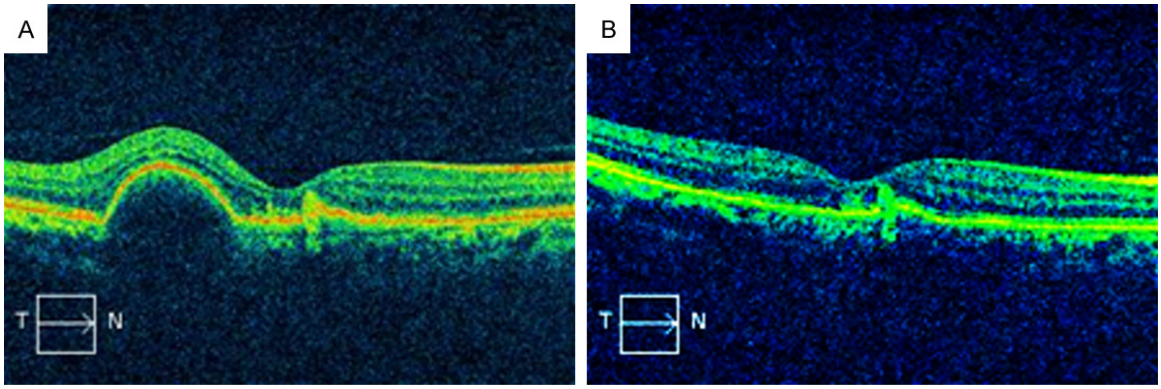

Figure 2. OCT Changes of the PED height (A: Before injection. B: The same patient after injection).

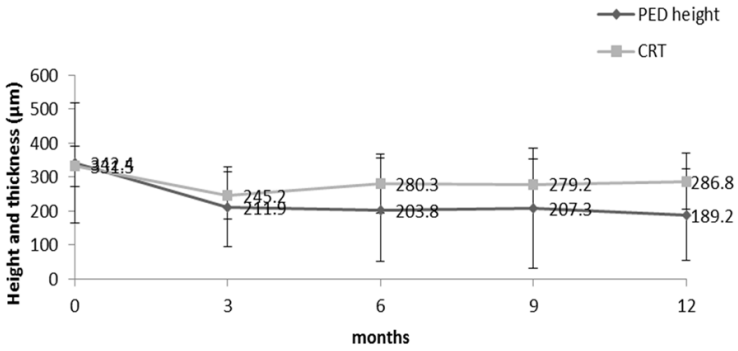

Figure 3. Change of the PED height and CRT.

first injection were 57.15 ± 12.13, 56.85 ± 10.74, and 58.46 ± 10.29, respectively. Compared to the baseline, there was significant improvement in the BCVA at every 3 months of follow-up (P = 0.003, P = 0.006 and P = 0.005, respectively, **Figure 1** and **Table 2**).

Opitical coherence tomography outcome

The mean maximum PED height was 342.38 ± 176.39 μm and 189.23 ± 134.69 μm at the baseline and month 12, respectively (z = -2.83, P < 0.05). One patient (7.7%) showed an increase in the PED height, whereas others (92.3%) had reductions (**Figure 2**). No patient showed complete resolvement in the PED

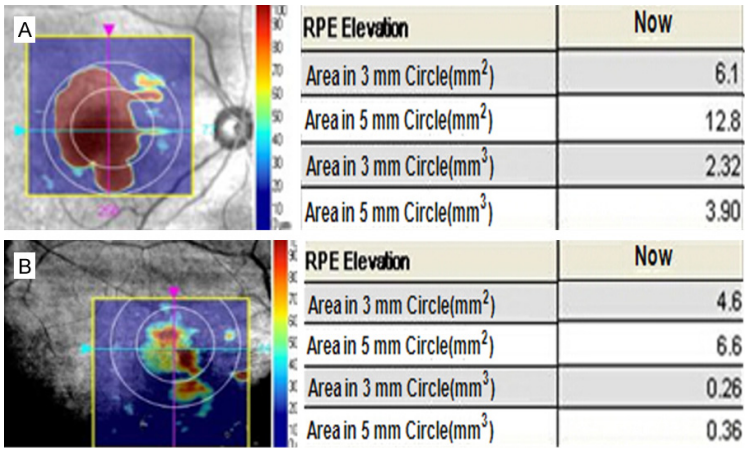

Figure 4. OCT Changes of the PED area and volume (A: Before injection. B: The same patient after injection).

height. The mean maximum PED heights at 3, 6 and 9 months after the first injection are shown in **Figure 3**. There was a statistically significant difference in each baseline-to-3-month follow-up interval (**Table 2**).

The mean PED area at the baseline and month 12 were 5.12 ± 4.69 mm^2 and 2.74 ± 2.89 mm^2, respectively ($z = -2.67$, $P < 0.05$). There was a statistically significant difference in each baseline-to-3-month follow-up interval (**Table 2**; **Figures 4**, **5**). The mean PED volume at the baseline and month 12 were 1.07 ± 1.73 mm^3 and 0.25 ± 0.46 mm^3, respectively ($z = -2.90$, $P < 0.05$, **Figure 4**). There was statistical significance between every 3-month follow-up and the baseline (**Table 2**; **Figure 5**).

The mean CRT decreased from 331.54 ± 60.08 μm at the baseline to 286.85 ± 82.47 μm at the last visit ($t = 1.85$, $P > 0.05$). The mean CRT was 245.15 ± 69.99 μm, 280.31 ± 86.81 μm and 279.15 ± 74.84 μm at 3, 6 and 9 months after the first injection, respectively (**Figures 3**, **6**). There was statistical significance between the 3-month and 6-month follow-ups and the baseline ($t = 4.12$, $P < 0.05$ and $t = 2.35$, $P < 0.05$, respectively).

There was no correlation between the PED height, area, volume, CRT and BCVA at the baseline and 12-month follow-up (**Table 3**).

Number of injections

The mean number of injections during the study period was 3.3 ± 1.1 (range, 1~5), and 23.1% (3/13) of the eyes had received less than 3 injections.

Complications

The treatment was well tolerated and there was no occurrence of infectious endophthalmitis, uveitis or an RPE tear during the follow-up period. Two eyes (15.3%) exhibited increased IOP on the day after the first injection, but it recovered to the normal level after treatment with eye drops.

Discussion

Retinal pigment epithelial detachment is a common feature of wAMD and an important predictor of vision loss in those patients. Approximately one-half of the patients with PED have experienced a mean visual loss of > 3 lines over a 12-month follow-up period. 8 Several treatments for PED including photodynamic therapy, intravitreal steroids or administration of bevacizumab have been attempted; however, the results are controversial [13-15]. Bevacizumab therapy has shown some functional benefits; however, the agent is expensive and not allowed in China.

Different studies have shown that ranibizumab is an effective treatment for wAMD [16-19]. Little is known regarding the effect of intravitreal ranibizumab as needed therapy for wAMD with PED. Inoue *et al*. [10] studied the response of different subtypes of PED to PRN injection after 3 loading doses of ranibizumab. They found that eyes with serous PED showed significant improvement in BCVA throughout the entire follow-up. All the eyes with serous PED and mixed PED showed a reduction of the maximum PED height by 100 μm or more. No subtype of PED height was shown to have been correlated with the final BCVA. Arora and Mckibbin [11] evaluated the effects of intravitreal ranibizumab with 3 consecutive monthly injections followed by as need therapy for large, serous PED secondary to AMD. They found 63% of the eyes had an increase in the ETDRS letter score from the baseline, and 26% eyes had a gain of 15 or more letters. The PED height did not flatten completely in any of the eyes. Giansanti *et al.* [12] reported different results. In their study, there was deterioration in BCVA (0.46 to 0.79 logMAR), an increase in the largest linear diameter of the PED (4499 to 5206

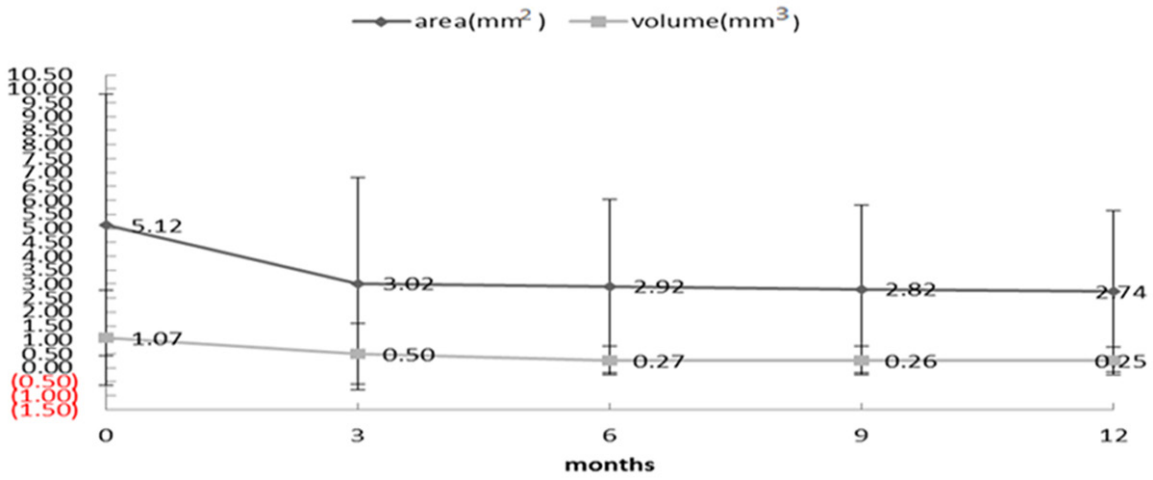

Figure 5. Change of the PED area and volume.

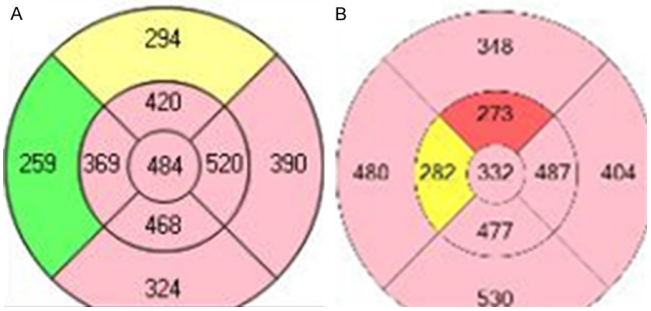

Figure 6. OCT Changes of the CRT (A: Before injection. B: The same patient after injection).

Table 3. The correlation between PED height, area, volume, CRT and BCVA

		PED height	PED area	PED volume	CRT
Baseline	r	-0.38	-0.41	-0.49	0.50
	P value	0.20	0.16	0.09	0.08
12 mo	r	-0.40	-0.43	-0.44	-0.41
	P value	0.18	0.15	0.13	0.17

μm) and a reduction in the maximum PED height (669 to 305 μm) at the 12-month follow-up. Because they performed quarterly follow-ups, the first signs of recurrence could have been missed.

Based on the above reasons, we used intravitreal ranibizumab as a PRN regimen after a first injection without 3 consecutive monthly injections for serous PED with wAMD and followed up monthly in our case series. All the patients avoided moderate visual loss at 12 months after the first injection. Additionally, 46.15% of the eyes had a gain of 15 or more ETDRS letters. Our visual acuity outcomes appeared to be better than those of Arora, 11 which might be because of their inclusion criteria for large serous PED. In our study, the mean maximum PED height and CRT showed a significant decrease at the first 3-months follow-up compared with the baseline. The mean PED height was sustained throughout the 12-month observation period, whereas the mean CRT was elevated at the 12-month follow-up.

Compared with other studies, we evaluated the PED area and PED volume in addition to the PED heights and CRT. They showed a significant reduction at the 3-month follow-up compared to the baseline and the results maintained until 12-month. This finding further confirmed the effective results of ranibizumab as needed therapy for PED with wAMD. Additionally, we found the same result as the afore mentioned studies in which there was no correlation between the PED height, area, volume, CRT and final BCVA, which might be because of 1) the small sample size of our study, 2) the relationship between the PED location and the macular, and 3) the course of the disease.

Adopted the strategy of pro re nata therapy, the number of injections in our study was less than that in the majority studies of three loading doze plus prn [11, 12]. However, the treatment effects in this study is as the same as others.

Although the number of injection in our study was the same as reported by Ach *et al*. [13], our outcomes was better than that study since their follow-up period was longer than ours. In our study, patients were followed up monthly, which help to observe the treatment effect and the disease progress and avoid irreversible damage.

The outcomes in this study showed the economy, efficacy and safety of intravitreal ranibizumab as needed therapy for serous PED with wAMD. We could attempt this administration because ranibizumab is expensive and is the only anti-VEGF agent in China. There are three patients received less than 3 times injections, and no patient needed reinjection because of enlargement of the PED size in the study. We recommend a prospective, multi-center, large sample size case series study for this type of disease.

Disclosure of conflict of interest

None.

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