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Effectiveness of Intravitreal Injection of Ranibizumab for Neovascular Age-Related Macular Degeneration with Serous Pigment Epithelial Detachment

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF 1,2 **Chun Zhao***
CD 1 **Zhen Zhang***
BCD 2 **Lei Chen**
AFG 1,2 **Fang Wang**
ACFG 2 **Ding Xu**

1 Department of Ophthalmology, Affiliated Shanghai Tenth Clinical Medical College of Nanjing Medical University, Nanjing, Jiangsu, P.R. China
2 Department of Ophthalmology, Tenth People's Hospital of Tongji University, Shanghai, P.R. China

* Chun Zhao and Zhen Zhang are co-first authors

Corresponding Author: Fang Wang and Ding Xu, e-mail: daisyxu70@hotmail.com
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Background: We sought to observe the effectiveness of intravitreal injection of ranibizumab in treating neovascular age-related macular degeneration (nAMD) with serous pigment epithelial detachment (sPED).

Material/Methods: A retrospective, noncomparative case series was performed. Twenty-3 eyes of 23 patients with sPED secondary to nAMD who had received intravitreal injections of ranibizumab were included in this study. All patients underwent best-corrected visual acuity (BCVA), synchronous fluorescein fundus angiography (FFA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT) examinations. All patients were treated with *pro re nata* intravitreal injections after 3 loading doses of ranibizumab and were followed up for 12 months. The differences in the BCVAs, maximum PED heights, PED volumes and CFTs of the affected eyes were compared between the baseline and last visit.

Results: Twelve months after the first injection, improved visual acuity was observed in 16 of the 23 eyes. 4 eyes exhibited stable visual acuity, and 3 eyes exhibited impaired visual acuity. The mean post-injection logMAR BCVA was 0.58±0.05, which was much better than that at baseline (0.76±0.08; t=1.751, P=0.0869). The mean maximum PED height at baseline was 350.17±35.73μm and it was decreased to 238.87±36.87μm (t=2.192, P=0.0337) at the last visit. The mean PED volume after injection was 0.34±0.1 mm^3, which was significantly decreased compared with that at baseline (0.81±0.21 mm^3; t=2.021, P=0.0494).The mean CFT decreased, but this difference was not statistically significant (t=1.003, P=0.3211). None of the patients exhibited endophthalmitis, uveitis or RPE tears.

Conclusions: Intravitreal injection of ranibizumab for the treatment of neovascular age-related macular degeneration with serous pigment epithelial detachment safely and effectively improved the patients' visual acuities and decreased their PED heights volumes.

MeSH Keywords: Intravitreal Injections • Macular Degeneration • Retinal Pigment Epithelium

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Background

Neovascular age-related macular degeneration (nAMD) is characterized by damage to photoreceptors and the retinal pigment epithelium (RPE) due to haemorrhaging and exudation caused by choroid neovascularization (CNV) [1]. Eyes with nAMD also often exhibit subretinal effusion and serous pigment epithelial detachment (sPED) because the volume of exudate resulting from CNV exceeds the range of RPE transfer [2]. According to many studies, vascular endothelial growth factor (VEGF) plays an important role in CNV formation and is the main pathological factor that contributes to vision loss in nAMD eyes. Intravitreal injections of anti-VEGF agents can improve the vision of affected eyes and reduce the rate of blindness [3]. However, reports on the effects of treating sPED-accompanied nAMD with intravitreal injections of anti-VEGF agents are still lacking. To address this gap, we administered intravitreal injections of ranibizumab to patients with sPED-accompanied nAMD and report the results herein.

Material and Methods

This was a retrospective, non-comparative study. Twenty-3 eyes of 23 patients treated between October 2011 and September 2013 were included. All of the patients were diagnosed with sPED-accompanied nAMD via synchronous FFA and ICGA at the Department of Ophthalmology of the Shanghai Tenth People's Hospital. This study was conducted according to the principles of the Declaration of Helsinki, and informed consent was obtained from all patients after the objective of the study was explained to them. This study was approved by the ethics committee of the Shanghai Tenth People's Hospital.

The recorded data included the best-corrected visual acuity (BCVA, based on the logarithmic visual acuity chart); intraocular pressure (IOP); ocular fundus condition; maximum PED height, PED volume, and central fovea thickness (CFT) and the presence of relevant ocular complications. Patients were evaluated at baseline and after each injection at monthly follow-ups. The best-corrected visual acuity, maximum PED height, PED volume and CFT at baseline and at the 12-month follow-up were compared. At the last visit, an increase in the reading of the visual acuity chart by 2 lines or more indicated visual improvement. A variation within 2 lines was considered to be indicative of stable vision, and a decrease of 2 lines or more indicated visual diminution.

All patients were treated with intravitreal ranibizumab (0.5 mg/0.05 ml, Lucentis, Novartis, Switzerland) *pro re nata* (PRN) after 3 loading doses. The patients were injected using a 30-guage needle through the pars plana under aseptic conditions in an operating room. Tobradex eye ointment was spread around the eyes after completion of the injections. No complications, such as intraocular haemorrhaging, were observed. After 3 loading doses, re-injection was performed if new subretinal fluid, retinal fluid accumulation, PED expansion or other CNV activities were present.

The exclusion criteria were as follows: polypoidal choroid vasculopathy (PCV) or retinal angiomatous proliferation (RAP) as diagnosed by FFA and ICG examination; PED without any evidence of CNV; haemorrhagic PED; mixed PED (co-existing fibrovascular and serous PED); co-existing ocular diseases, such as glaucoma or diabetic retinopathy; or the receipt of previous treatments for AMD [4].

For recording, the best-corrected visual acuity results were converted to the logarithm of the minimum angle of resolution (logMAR). A Spectralis HRA instrument (Heidelberg, Germany) was used to conduct the synchronous FFA and ICGA examinations, and a Cirrus HD-OCT 5000 imager (Carl Zeiss, Germany) was used to detect retinal morphological alternations in the macular region, to measure the PED volume and the CFT via the macular thickness protocol and to apply the RPE analysis protocol with 6-mm horizontal and vertical line scans. The scanning depth was 2 mm and the scanning length was adjusted according to the range of the lesion (6–9 mm). The image resolution was 512×128 pixels. 5-line 0.25×6 mm scanning was performed at the highest point of the PED, the vertical height of which was measured manually on the OCT monitor using the built-in manual calliper tool. An advanced RPE analysis system was used to manually select the pre- and post-treatment PED images. The volume of a 5-mm circle was chosen to compare the results. The cube mode was used for the CFT measurements, and the scanning line was 6 mm long. The reclosing mode was adopted for each patient and each measurement.

SPSS 17.0 software was used to conduct statistical analyses, and paired *t*-tests were performed to compare the pre- and post-treatment BCVAs, PED heights, PED volumes and CFTs. $P<0.05$ was considered to indicate a statistically significant difference.

Results

A total of 23 eyes of 23 Chinese patients were included in this study. The baseline characteristics are shown in Table 1.

At the 12-month follow-up, visual improvement was observed in 16 (69.6%) eyes, stable vision was observed in 4 (17.4%) eyes, and decreased vision was noted in 3 (13%) eyes. The average logMAR BCVA increased from 0.76±0.08 to 0.58±0.05, but this difference was not statistically significant ($t=1.751$, $P=0.0869$).

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Table 1. Baseline characteristics of all studied eyes.

Injected eye, n	23
Right, n (%)	17 (73.9%)
Left, n (%)	6 (26.1%)
Number of patients	23
Male, n (%)	15 (65.2%)
Female, n (%)	8 (34.8%)
Age (years), mean±SD (range)	69.69±1.47 (56–80)

As revealed by fundus examination, posterior pole retina of the affected eyes flattened after injections (Figures 1, 2) Synchronous FFA and ICGA examinations found that among the 23 eyes, fluorescein leakage significant alleviation occurred in 18 eyes, no improvement or deterioration appeared in 5 eyes.

The average CFTs at baseline and at the last visit were 324.56±16.42 μm and 299.82±18.39 μm, respectively. The mean decrease in the CFT was 24.73±19.04 μm. There was no significant difference between the CFT values at baseline and at the last visit (t=1.003; P=0.3211).

Of the 23 eyes, 15 (65.2%) exhibited a significant decrease in the maximum PED height (range >100 μm) and only 3 (13%) exhibited almost no change in this height. The average maximum PED height sharply decreased from 350.17±35.73 μm to 238.87±36.87 μm compared with the baseline value, and this difference was statistically significant (t=2.192; P=0.0337).

The average PED volumes at baseline and at the 12-month visit were 0.81±0.21 mm^3 and 0.34±0.1 mm^3, respectively. The average decrease was 0.47±0.15 mm^3, and this decrease was also statistically significant (t=2.021; P=0.0494).

After 12 months of follow-up, a total of 101 injections and an average of 4.39±0.26 injections per patient had been administered. Of the 23 eyes, 15 (65.2%) were injected more than 3 times.

One (4.3%) eye exhibited increased IOP on the day after the first injection, but it recovered to the normal level after treatment with eye drops. None of the patients experienced endophthalmitis, uveitis, RPE tears or any other severe adverse ocular reactions during the follow-up period.

Discussion

Age-related macular degeneration (AMD) is the main cause of practical and irreversible central blindness in patients after the age of 50 years [5,6]. Neovascular age-related macular degeneration, also known as exudative AMD, has a long natural course that involves repeated haemorrhages in the macular area and a poor prognosis in terms of visual acuity. This condition is primarily characterized by neovascularization of choroid in the macular area and the abnormal growth of this structure towards the retina, leading to changes, such as the accumulation of subretinal fluid, haemorrhaging and retinal pigment epithelium detachment [7]. Vascular endothelial growth factor (VEGF) is the most important angiogenic factor, and its key role in the formation of CNV has been confirmed [8]. Presence of increased VEGF levels in AMD led to the use of anti-VEGF therapy in this condition [9]. nAMD is the first indication for the administration of anti-VEGF agents via intraocular injection. The use of this treatment as a monotherapy has been demonstrated to be more effective [10] in terms of anti-VEGF activity than its combination with PDT or PDT alone in multicentre randomized controlled clinical studies [11].

The retinal pigment epithelium (RPE) is an important tissue that maintains the metabolism of the neurosensory retina and ensures its sensitization. Under normal conditions, the RPE is closely linked to and constitutes part of the blood-retina barrier. Moreover, the RPE layer is tightly connected to the Brunch membrane, which prevents the physiological transudate of the choroid vessel from entering the retinal neuroepithelial layer. In nAMD, the abnormal growth of choroidal neovascularization may cause the connection between the RPE and Brunch membrane to become flabby, resulting in PED and severely impaired visual acuity. Researchers [12] have found that after 1 year, the visual acuities of approximately half of PED patients decline by 3 lines if no intervention is applied. Therefore, PED is often considered a complication of nAMD and is indicative of severe nAMD with poor prognosis.

PED has many manifestations that can be classified into 4 categories according to the FFA results: the drusen type, serous type, fibre exudative type, and haemorrhagic type [1]. Serous PED is the most common type. Reported PED treatments include PDT, intraocular injections of anti-VEGF agents, intraocular injections of steroids, and other treatments [13–15]. Although the treatment of this condition has been reported by many authors, the curative efficacies of these treatments remain controversial, and the relevant studies often have small sample sizes.

Arora and Mckibbin [16] administered 3 monthly injections to nAMD patients with accompanying serous PED and found that the ETDRS letter scores increased in 63% of the patients, and 26% experienced a gain of 15 letters or more. These findings are consistent with our results. In our study, the visual acuities of 20 (86.9%) of the patients were protected.

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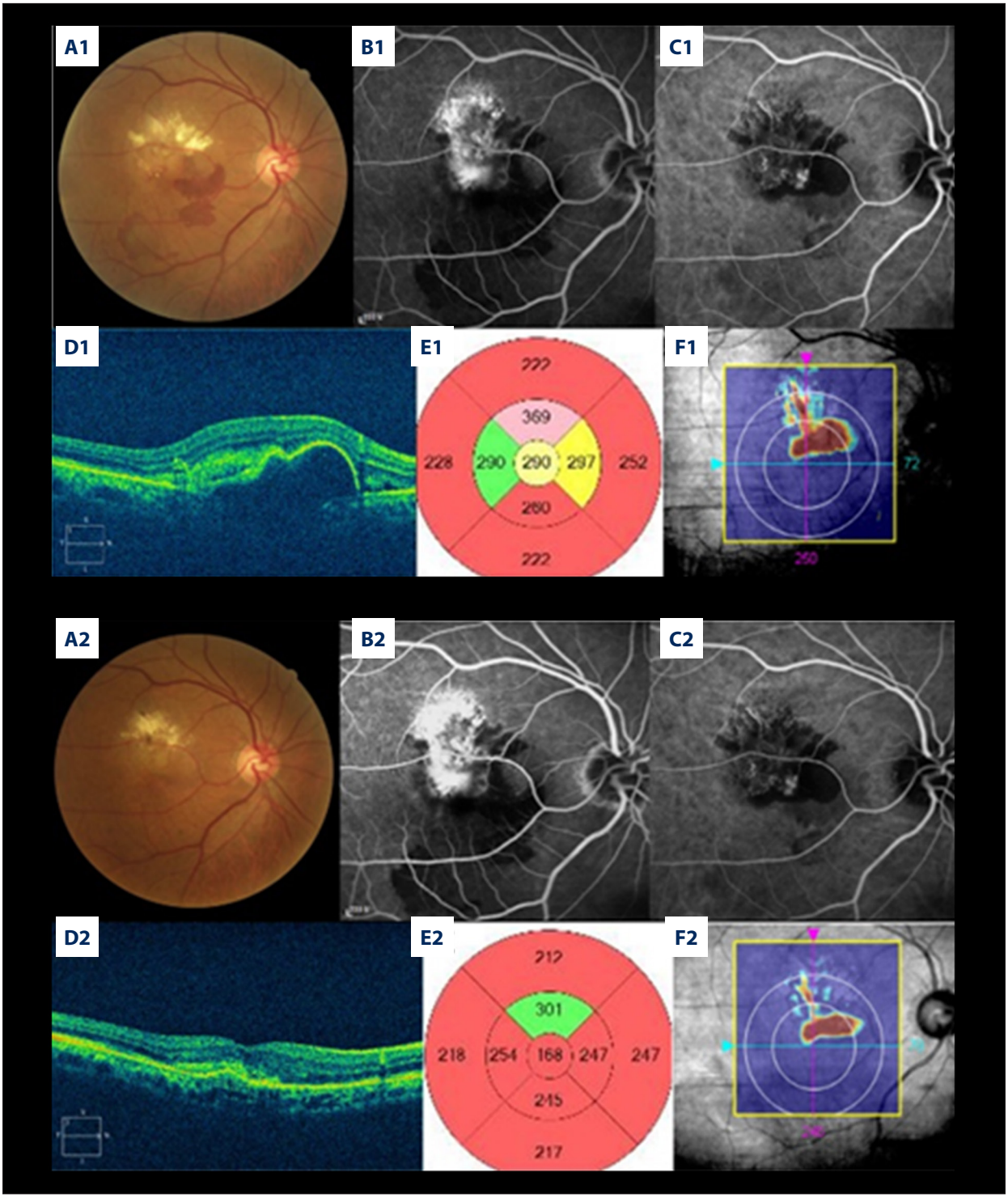

Figure 1. Case-1: A 61-year-old man with a diagnosis of nAMD with sPED. (**A1–F1**) Images at baseline. (**A2–F2**) Images at the 12-month follow-up. (**A1, A2**) Colour photo of the fundus of the affected eye. (**B1, B2**) Fluorescein fundus angiography (FFA). (**C1, C2**) Indocyanine green angiography (ICGA) image from the FFA phase. (**D1, D2**) PED height detected by OCT. (**E1, E2**) Central fovea thickness analysis (CFT). (**F1, F2**) Volume of the PED in the 5-mm circle.

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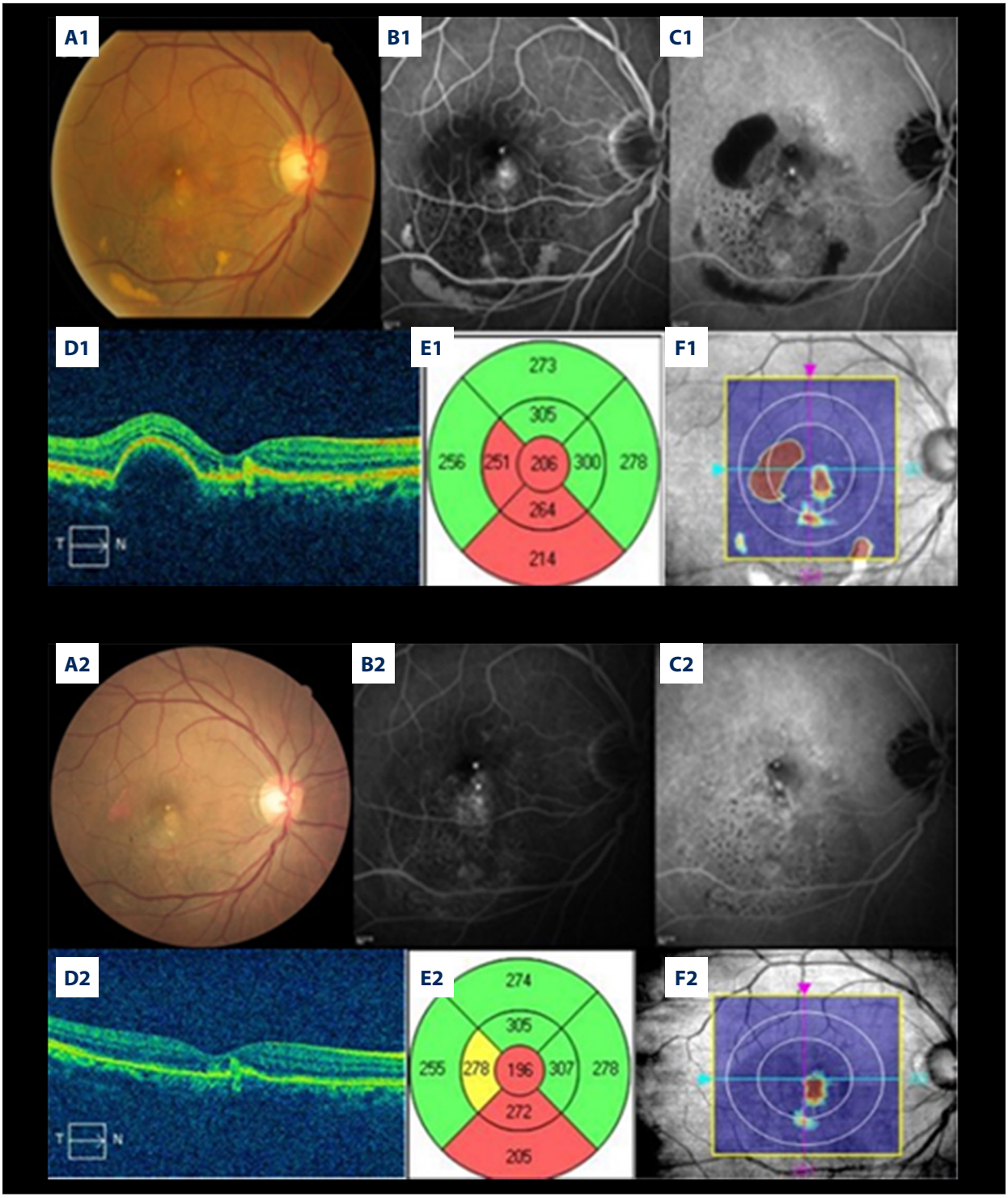

Figure 2. Case-2: A 73-year-old man with a diagnosis of nAMD with sPED. (**A1–F1**) Images at baseline. (**A2–F2**) Images at the 12-month follow-up.

Inoue et al. [17] administered ranibizumab injections to patients with different types of PED and observed the best curative effects occurred in the patients with serous PED. Consistent with our results, the mean maximum PED height of the serous PED patients decreased by more than 100 μm following treatment. In our study, the average reduction in PED height was 111.3±32.8 μm. Of the 23 patients, 15 (65.2%) exhibited a significant decrease, defined as a decrease of more than 100 μm.

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In contrast with other studies, we simultaneously measured PED volumes and found that they were also significantly decreased at the last visit. This finding further supports the effectiveness of the treatment.

Anti-VEGF agents have demonstrated efficacy in the treatment of nAMD, but their short duration of action necessitates repeated injections, which might increase the risk of endophthalmitis. Therefore, standard treatment and follow-up are crucial for achieving a good prognosis in terms of visual acuity [18]. Chang et al. [19] and Kaiser et al. [20] adopted a regimen of monthly ranibizumab injections in 2 stage III clinical trials. Patients' visual acuities obviously increased at 3 months after treatment, and these improvements were subsequently maintained. To reduce the frequency of re-treatment, Menke et al. [21], Schmidt et al. [22] and Rosenfeld et al. [23] extended the interval between treatment and follow-up to 3 months and found that monthly follow-ups were much better than quarterly follow-ups for enhancing and maintaining visual acuity. Furthermore, the visual acuity improvements observed following the first 3 treatments performed on a quarterly basis were not maintained in subsequent follow-ups. Based on the instructions of Lucentis in China, our study involved a loading phase of 3 consecutive monthly injections and monthly follow-ups. Repeated injections were administered based on OCT findings.

In our study, the CFTs of the affected eyes decreased compared with the baseline values after treatment, but this difference was not statistically significant. This lack of effect might have been due to the short follow-up time, the small sample size or the non-randomized nature of the study.

In this study, a total of 101 injections were administered, and each eye received an average of 4.4 injections. These results are similar to those of Arora [16] who reported an average of 5.4 injections. In our study, 15 (65.2%) eyes were injected more than 3 times, but no endophthalmitis, uveitis or RPE tears were observed, indicating that intravitreal injection of ranibizumab is a safe method for treating nAMD accompanied by serous PED.

The results revealed that the BCVAs increased significantly, the subretinal and retinal fluids were absorbed, and the maximum PED height and volume clearly improved and stabilized following treatment. These findings suggest that ranibizumab elicits good therapeutic effects in nAMD accompanied by serous PED. Ranibizumab obviously improved both the patients' clinical manifestations and their examination results. Thus, the clinical use of ranibizumab should be further promoted.

However, this study has some limitations, which include the following: (1) this was a non-multiple centre study with a small sample size and a short follow-up time; (2) no subgroup analyses according to the extent of PED were performed due to the limited number of cases; (3) no analyses of the effects of the disease course on treatment outcome were performed; and (4) no comparisons with other treatments, such as on-demand (PRN) administration of anti-VEGF agents and PDT were made. Therefore, determination of whether this unique and simple anti-VEGF treatment (i.e., 3 loading doses + PRN) is the best treatment regimen for this type of AMD and whether the combination of this treatment with PDT or other treatments are more economical and effective will require further randomized, multicentre studies with larger sample sizes. Such studies are our goal for the future.

Conclusions

Intravitreal injection of ranibizumab is a safe and effective method for treating nAMD accompanied by serous PED. This therapy can improve patients' vision, decrease the height and volume of sPED and decrease the thickness of CFT and should therefore be widely used.

Competing interests

The authors declare that they have no competing interests.

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