

## ORIGINAL ARTICLE

# Therapeutic effect of Ranibizumab combined with Triamcinolone Acetonide on wet age-related macular degeneration and its effect on interleukin

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**Received:** August 5, 2020

**Accepted:** October 21, 2020

**Online Published:** November 11, 2020

**DOI:** 10.5430/dcc.v7n2p18

**URL:** <https://doi.org/10.5430/dcc.v7n2p18>

## ABSTRACT

**Objective:** To observe the clinical efficacy of ranibizumab combined with triamcinolone acetonide on wet age-related macular degeneration (AMD) and explore the effect of this method on the levels of IL-1 $\beta$ , IL-2, IL-6 and IL-8.

**Methods:** Prospective study was conducted in this research. 86 cases of patients with wet AMD (102 eyes) admitted in Baogang Hospital of Inner Mongolia from November 2017 to October 2018 were chosen and randomly divided into the ranibizumab group (43 cases, 50 eyes) and the combination group (43 cases, 52 eyes). The ranibizumab group of patients were given intravitreal injection of ranibizumab, and the combination group was additionally given triamcinolone acetonide on the basis of the ranibizumab group. The intraocular pressure values of the two groups before treatment, in 2 weeks, 1 month and 3 months after treatment were compared. The central macular thickness (CMT) and visual acuity of the two groups before treatment as well as in 1 month, 3 months and 6 months after treatment were compared. The levels of IL-1 $\beta$ , IL-2, IL-6 and IL-8 in the serum were compared between the two groups before treatment and in 1 month after treatment. The incidences of complications during treatment in the two groups were recorded and compared. The data were analyzed by use of *t*-test, repeated measures ANOVA and  $\chi^2$  test.

**Results:** There were no statistically significant differences in intraocular pressure value between the two groups ( $F_{groups} = 1.275, p = .496; F_{time} = 1.810, p = .211; F_{interaction} = 1.772, p = .335$ ). There were no statistically significant differences in CMT and visual acuity before treatment between the two groups ( $t = 0.042, p = .967; t = 0.720, p = .473$ ). In one month, three months and six months after treatment, CMT in the combined group was lower than that in the ranibizumab group ( $t = 2.086, p = .039; t = 3.398, p = .001; t = 2.987, p = .004$ ), and the visual acuity of the combined group was higher than that of the ranibizumab group ( $t = 3.265, p = .001; t = 2.217, p = .029; t = 2.519, p = .013$ ). CMT showed a decreasing tendency ( $t_{before\ treatment\ vs.\ t_1\ month\ after\ treatment} = 6.210, 4.218, p < .001; t_1\ month\ after\ treatment\ vs.\ t_3\ months\ after\ treatment = 16.772, 15.865, p < .001; t_3\ months\ after\ treatment\ vs.\ t_6\ months\ after\ treatment = 4.472, 4.848, p < .001$ ) and the visual acuity showed an increasing trend ( $t_{before\ treatment\ vs.\ t_1\ month\ after\ treatment} = 4.527, 8.395, p < .001; t_1\ month\ after\ treatment\ vs.\ t_3\ months\ after\ treatment = 5.369, 5.349, p < .001; t_3\ months\ after\ treatment\ vs.\ t_6\ months\ after\ treatment = 3.335, 3.730, p < .001$ ) with the time going by in the two groups. Compared with the indicators before treatment, the levels of IL-1 $\beta$ , IL-6 and IL-8 in the serum in 1 month after treatment were lower in both two groups ( $t_{combination\ group} = 10.544, 32.169, 33.156, all\ p < .001; t_{ranibizumab\ group} = 8.996, 25.687, 30.754, all\ p < .001$ ), and these indicators in the combination group were lower than those in the ranibizumab group ( $t = 2.894, p = .005; t = 5.997, p < .001; t = 3.934, p < .001$ ). Compared with the indicators before treatment, the levels of IL-2 in the serum in 3 months after treatment in the two groups were higher ( $t = 20.067, 9.091, all\ p < .001$ ).

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$p < .001$ ), and the indicator in the combination group was higher than that in the ranibizumab group ( $t = 7.705$ ,  $p < .001$ ). There were no statistically significant differences in the incidences of bleeding, intraocular foreign body sensation and transient high IOP and the total incidence of complications between the two groups (correction  $\chi^2 = 0.001$ ,  $p = .972$ ; correction  $\chi^2 = 0.221$ ,  $p = .638$ ; Fisher's exact test  $p = .116$ ; correction  $\chi^2 = 0.004$ ,  $p = .951$ ).

**Conclusions:** Intravitreal injection of ranibizumab combined with triamcinolone acetonide can effectively improve the visual function of wet AMD, reduce CMT and the levels of IL-1 $\beta$ , IL-6 and IL-8 in the serum, increase the level of IL-2 in the serum and relieve the degree of inflammatory responses.

**Key Words:** Ranibizumab, Triamcinolone acetonide, Age-related macular degeneration, Interleukin

## 1. INTRODUCTION

Age-related macular degeneration (AMD) is a clinically commonly seen age-related degenerative eye disease, and it is also one of important causes which lead to blindness. According to the statistics,<sup>[1]</sup> the incidence of AMD in the senior in China is around 16.5%, and it has been increasing year by year with the aging population larger. On the basis of the pathological changes, AMD can be divided into two types: dry AMD and wet AMD. The former is progressed slowly with a good prognosis, but the latter one is progressed quickly with a high rate of blindness, which can lead to a sharp decrease in patients' life quality.<sup>[2]</sup> At present, vascular endothelial growth factor (VEGF) is a main treatment method for wet AMD, and ranibizumab belongs to VEGF family. It can effectively inhibit the angiogenesis in order to improve the visual acuity. However, some patients still show an unsatisfactory clinical efficacy. Nevertheless, the effect of ranibizumab on chronic ocular inflammation remains unclear.<sup>[3]</sup> Triamcinolone acetonide, a type of corticosteroid, can effectively reduce vascular permeability in order to relieve macular edema and play an exact role in anti-inflammation.<sup>[4]</sup> In this research, ranibizumab was applied in combination with triamcinolone acetonide to the treatment of 43 cases of wet AMD, and the clinical efficacy and its effect on the levels of IL-1 $\beta$ , IL-2, IL-6 and IL-8 were compared with those of ranibizumab alone in order to explore a better therapeutic schedule.

## 2. OBJECTS AND METHODS

### 2.1 Objects

Inclusion criteria: 1) patients who were up to the diagnostic standards of wet AMD<sup>[5]</sup> and confirmed by imageological examinations; 2) patients with vision loss. Exclusion criteria: 1) patients with other types of eye diseases; 2) patients with a medical history of eye trauma and eye surgery; 3) patients with severe hepatic and renal dysfunction, malignant tumors and allergic constitution; 4) patients who took hormone drugs or anti-VEGF drugs within one month before treatment; 5) patients with active infectious diseases at other parts.

86 cases of patients with wet AMD (102 eyes) admitted in Baogang Hospital of Inner Mongolia from November 2017 to October 2018 were chosen and randomly divided into the ranibizumab group and the combination group. There were 43 cases (50 eyes) in the ranibizumab group, including 23 cases of male patients (26 eyes) and 20 cases of female patients (24 eyes), aged 50-80 ( $63.2 \pm 7.0$ ), with a course of 6-21 ( $13.5 \pm 2.4$ ) years. There were 43 cases (52 eyes) in the combination group, including 24 cases of male patients (28 eyes) and female patients (24 eyes), aged 50-80 ( $63.9 \pm 7.2$ ), with a course of 6-20 ( $12.9 \pm 2.6$ ) years. There was no statistically significant difference in general data (such as sex constituent ratio and age) between two groups of patients ( $p > .05$ ). This research complied with "Declaration of Helsinki", and all patients were required to sign informed consent forms.

### 2.2 Treatment methods

Each patient in the ranibizumab group was given intravitreal injection of ranibizumab: the operation eye was treated with tobramycin eye drops for 3 days before surgery, 3 times per day; the conventional eye area disinfection was conducted before operation, with proparacaine hydrochloride used in local anesthesia, 0.05 ml of ranibizumab injection (Novartis, Approval No.: S20110085, specification: 10 mg/ml) was injected slowly with the syringe needle vertically thrusting into the vitreous cavity from pars plana at the latter 4 mm of infratemporal corneal limbus. After the needle was pulled out, sterile cotton swabs were used for pressing the needle eye for 3 s. After operation, it was required to check if bleeding or drug leakage occurred. This medicine should be used once every four weeks, 3 times in total. On the basis of the treatment given to the ranibizumab group, each patient in the combination group was additionally given 0.05 ml of triamcinolone acetonide (Kunming Jida Pharmaceutical Co., Ltd., SFDA Approval No.: H53021604, specification: 40 mg/ml) in the same way as ranibizumab was used, once every four weeks. Both of the two groups were given antibiotic eye drops for treatment after operation.

**2.3 Indicator observation**

**2.3.1 The comparison in intraocular pressure values before and after treatment**

CT80 Non-contact Automatic Tonometer (Topcon, Japan) was used to measure intraocular pressure values of the two groups before treatment, in 2 weeks, 1 month and 3 months after treatment. The measurement was continuously made three times, and the results were averaged and recorded.

**2.3.2 The comparison in central macular thickness (CMT) before and after treatment**

OCT-100 Optical Coherence Tomography (Topcon, Japan) was used to detect CMT of the two groups before treatment as well as in 1 month, 3 months and 6 months after treatment. Before examination, each patient was required to receive an adequate mydriasis and adapt in the darkroom for 30 min. The suitable eye position was chosen in order to acquire a clear image of retina, and the scanning mode was set up in order to swiftly scan macular volume and acquire a high-intensity signal image. The default software can make a stratified analysis of retina and define the distance between the inner limiting membrane and the retinal pigment epithelium (RPE) – Bruch’s membrane complex as CMT.

**2.3.3 The comparison in visual acuity before and after treatment**

The five-grade notation of visual acuity chart was used to record the visual acuity of the two groups before treatment as well as in 1 month, 3 months and 6 months after treatment.

**2.3.4 The comparison in the levels of IL-1β, IL-2, IL-6 and IL-8 in the serum before and after treatment**

Before treatment and in 1 month after treatment, 5 ml of fasting blood was taken from each patient in the two groups respectively, and the supernatant was taken after 8-min centrifugation at the rotate speed of 3,000 r/min. Enzyme linked immunosorbent assay (ELISA) was used to measure the levels of IL-1β, IL-2, IL-6 and IL-8 in the serum. All ELISA kits were purchased from Shanghai Huiying Biological Tech-

nology Co., Ltd., and the experimental procedures should be strictly followed according to the kit instructions. The microplate reader was used to measure optical density (OD) of the sample to be tested, and the concentration of the indicator to be measured was required to be calculated according to the standard curve.

**2.3.5 The comparison in the incidence of complications**

It was required to make statistics of the incidence of the complications (such as bleeding, intraocular foreign body sensation and transient high IOP) in the two groups of patients during the process of treatment and the follow-up visit.

**2.4 Statistical methods**

Prospective study was conducted in this research. SPSS 24.0 statistical software was applied to statistical analysis, and the measurement data were represented by mean ± standard deviation. Independent samples *t*-test or paired *t*-test was applied to the comparison between the two groups; repeated measures ANOVA was used in the comparison of repeated measurement data, and the further comparison of two samples was made by use of LSD-*t* test. The categorical data was represented by [n (%)], when the comparison was made between the two groups, Fisher’s exact test was used if the theoretical frequency was lower than 1, correction  $\chi^2$  was used if the theoretical frequency was between 1 and 5, and  $\chi^2$  was used if the theoretical frequency was more than 5. The difference ( $p < .05$ ) was of statistical significance.

**3. RESULTS**

**3.1 The comparison in intraocular pressure values before and after treatment**

There was no statistically significant difference in intraocular pressure value between the ranibizumab group and the combination group ( $F_{groups} = 1.275, p = .496; F_{time} = 1.810, p = .211; F_{interaction} = 1.772, p = .335$ ). See Table 1 for details.

**Table 1.** The comparison in intraocular pressure value before and after treatment between the ranibizumab group and the combination group (mmHg)

Groups	Eyes	Before treatment	2 weeks after treatment	1 month after treatment	3 months after treatment
Ranibizumab	50	15.7±3.0	16.6±3.2	15.7±2.2	15.8±2.0
Combination	52	15.7±2.8	16.2±3.1	15.7±2.4	15.8±2.1

Note. Data were expressed as means ± standard deviation.  $F_{groups} = 1.275, p = .496; F_{time} = 1.810, p = .211; F_{interaction} = 1.772, p = .335$ . 1 mmHg = 0.133 kPa.

**3.2 The comparison in CMT before and after treatment**

There was a statistically significant difference in CMT between the ranibizumab group and the combination group ( $F_{groups} = 12.421, p < .001; F_{time} = 25.119, p < .001;$

$F_{interaction} = 18.452, p < .001$ ); there was no statistically significant difference in CMT before treatment between the two groups ( $t = 0.042, p = .967$ ); in 1 month, 3 months and 6 months after treatment, CMT of the combination

group was lower than that of the ranibizumab group ( $t = 2.086, p = .039; t = 3.398, p = .001; t = 2.987, p = .004$ ); both of the two groups showed a decreasing tendency in CMT with the time going by ( $t_{before\ treatment}$  vs.  $t_{1\ month\ after\ treatment} = 6.210, 4.218, p < .001; t_{1\ month\ after\ treatment}$  vs.  $t_{3\ months\ after\ treatment} = 16.772, 15.865, p < .001; t_{3\ months\ after\ treatment}$  vs.  $t_{6\ months\ after\ treatment} = 4.472, 4.848, p < .001$ ). See Table 2 for details.

**3.3 The comparison in visual acuity before and after treatment**

There was a statistically significant difference in visual acuity between the ranibizumab group and the combination group ( $F_{groups} = 23.179, p < .001; F_{time} = 35.871, p < .001; F_{interaction} = 30.114, p < .001$ ); there was no statistically significant difference in visual acuity before treatment between the two groups ( $t = 0.720, p = .473$ ); in 1 month, 3 months and 6 months after treatment, the visual acuity in the combination groups was higher than that in the ranibizumab group ( $t = 3.265, p = .001; t = 2.217, p = .029; t = 2.519, p = .013$ ); both of the two groups showed an increasing tendency in visual acuity with the time going by ( $t_{before\ treatment}$  vs.  $t_{1\ month\ after\ treatment} = 4.527, 8.395, p < .001; t_{1\ month\ after\ treatment}$  vs.  $t_{3\ months\ after\ treatment} = 5.369, 5.349, p < .001; t_{3\ months\ after\ treatment}$  vs.  $t_{6\ months\ after\ treatment} = 3.335, 3.730, p < .001$ ). See Table 3 for details.

**3.4 The comparison in the levels of IL-1β, IL-2, IL-6 and IL-8 in the serum before and after treatment**

There was no statistically significant difference in the levels of IL-1β, IL-2, IL-6 and IL-8 in the serum before treatment between the ranibizumab group and the combination group ( $t = 0.077, p = .939; t = 0.467, p = .641; t = 0.147, p = .884; t = 0.169, p = .886$ ); in 1 month after treatment, the levels of IL-1β, IL-6 and IL-8 in the serum in the two groups were lower ( $t_{combination\ group} = 10.544, 32.169, 33.156, all p < .001; t_{ranibizumab\ group} = 8.996, 25.687, 30.754, all p < .001$ ), and the levels of IL-2 in the two groups were higher ( $t_{combination\ group} = 20.067, p < .001; t_{ranibizumab\ group} = 9.091, p < .001$ ); the levels of IL-1β, IL-6 and IL-8 in the serum in 1 month after treatment in the combination group were lower than those in the ranibizumab group ( $t = 2.894, p = .005; t = 5.997, p < .001; t = 3.934, p < 0.001$ ), and the level of IL-2 in 1 month after treatment in the combination group was higher than that in the ranibizumab group ( $t = 7.705, p < .001$ ). See Tables 4-5 for details.

**3.5 The comparison in the incidence of complications**

There were no statistically significant differences in the incidence of bleeding, intraocular foreign body sensation and transient high IOP and the total incidence of complications between the ranibizumab group and the combination group (correction  $\chi^2 = 0.001, p = .972$ ; correction  $\chi^2 = 0.221, p = .638$ ; Fisher's exact test  $p = .116$ ; correction  $\chi^2 = 0.004, p = .951$ ). See Table 6 for details.

**Table 2.** The comparison in CMT before and after treatment between the ranibizumab group and the combination group ( $\mu\text{m}$ )

Groups	Eyes	Before treatment	1 month after treatment	3 months after treatment	6 months after treatment
Ranibizumab	50	422±65	373±52 <sup>#</sup>	234±34 <sup>#c</sup>	202±32 <sup>#&amp;^</sup>
Combination	52	422±63	351±50 <sup>*#</sup>	212±32 <sup>*#&amp;</sup>	184±29 <sup>*#&amp;^</sup>

Note. Data were expressed as means ± standard deviation.  $F_{groups} = 12.421, p < .001; F_{time} = 25.119, p < .001; F_{interaction} = 18.452, p < .001$ . Compared with the ranibizumab group, <sup>\*</sup> $p < .05$ ; compared with the indicators before treatment, <sup>#</sup> $p < .05$ ; compared with the indicators in 1 month after treatment, <sup>c</sup> $p < .05$ ; compared with the indicators in 3 months after treatment, <sup>&</sup> $p < .05$ .

**Table 3.** The comparison in visual acuity before and after treatment between the ranibizumab group and the combination group

Groups	Eyes	Before treatment	1 month after treatment	3 months after treatment	6 months after treatment
Ranibizumab	50	4.2±0.2	4.4±0.2 <sup>#</sup>	4.6±0.2 <sup>#c</sup>	4.7±0.2 <sup>#&amp;^</sup>
Combination	52	4.2±0.1	4.5±0.2 <sup>*#</sup>	4.7±0.2 <sup>*#&amp;</sup>	4.8±0.2 <sup>*#&amp;^</sup>

Note. Data were expressed as means ± standard deviation.  $F_{groups} = 23.179, p < .001; F_{time} = 35.871, p < .001; F_{interaction} = 30.114, p < .001$ . Compared with the ranibizumab group, <sup>\*</sup> $p < .05$ ; compared with the indicators before treatment, <sup>#</sup> $p < .05$ ; compared with the indicators in 2 weeks after treatment, <sup>c</sup> $p < .05$ ; compared with the indicators in 1 month after treatment, <sup>&</sup> $p < .05$ .

**4. DISCUSSION**

Wet AMD, which is also named neovascular AMD, has been a main disease that causes the senior blind in the world-wide. This disease has a complicated pathogenesis, which

involves inflammatory responses, oxidative stress responses, the generation of VEDF and other aspects. It is mainly characterized by main pathological changes such as macular drusen, choroidal neovascularization and photoreceptor

in geographic atrophy, intensively affecting patients' visual acuity.<sup>[6,7]</sup> In recent years, multiple drugs and different drug administration methods have been applied to the treatment of wet AMD, for example, periocular or intravitreal injection of hormones and VEGF inhibitors. They have a remarkable

improvement effect on macular oedema in patients with wet AMD.<sup>[8]</sup> Past studies<sup>[9]</sup> have shown that the visual function in patients with wet AMD is effectively improved after the intravitreal injection of ranibizumab, but the therapeutic effect still remains to be improved.

**Table 4.** The comparison in the levels of IL-1β and IL-2 before and after treatment between the ranibizumab group and the combination group (ng/L)

Groups	Eyes	IL-1β		t	p	IL-2		t	p
		Before treatment	1 month after treatment			Before treatment	1 month after treatment		
Ranibizumab	50	14.8±3.9	9.6±1.2	8.996	<.001	20.4±2.2	26.9±4.6	9.091	<.001
Combination	52	14.9±3.9	8.8±1.3	10.544	<.001	20.2±2.4	33.6±4.2	20.067	<.001
t		0.077	2.894			0.467	7.705		
p		.939	.005			.641	<.001		

Note. IL-1β, interleukin-1β; IL-2, interleukin-2

**Table 5.** The comparison in the levels of IL-6 and IL-8 in the serum before and after treatment between the ranibizumab group and the combination group (ng/L)

Groups	Eyes	IL-6		t	p	IL-8		t	p
		Before treatment	1 month after treatment			Before treatment	1 month after treatment		
Ranibizumab	50	45.2 ± 5.2	23.5±2.9	25.687	<.001	41.6 ± 4.4	20.4±2.2	30.754	<.001
Combination	52	45.3 ± 5.1	20.5±2.0	32.619	<.001	41.7 ± 4.6	18.7±2.1	33.156	<.001
t		0.147	5.997			0.169	3.934		
p		.884	<.001			.866	<.001		

Note. IL-6, interleukin-6; IL-8, interleukin-8

**Table 6.** The comparison in the incidence of complications between the ranibizumab group and the combination group [n (%)]

Groups	Eyes	Bleeding	Foreign body sensation	Transient high IOP	Total Incidence
Ranibizumab	50	1 (2.00)	1 (2.00)	2 (4.00)	4 (8.00)
Combination	52	2 (3.85)	3 (5.77)	0 (0.00)	5 (9.62)
Correction $\chi^2$		0.001	0.221	-	0.004
p		.972	.638	.116	.951

Note. n: the number of eyes.

Wet AMD is progressed with the hyperplasia of new vessels in the pigment epithelium layer, leading to the formation of choroid and then causing macular oedema and larger CMT. Furthermore, it can also induce pigment epithelial cells to separate from neuroepithelial cells, leading to vision loss. Therefore, CMT and visual acuity are important indicators to evaluate the clinical efficacy.<sup>[10]</sup> Ranibizumab is a type of angiogenesis inhibitor which is formed due to the combination of VEGF-A isomer antibody fragment and monoclonal antibody. It can inactivate VEGF by inhibiting the mitosis of endothelial cells, and it is a commonly-used anti-VEGF drug in the aspect of ophthalmology.<sup>[11]</sup> Triamcinolone acetonide

is a clinical anti-inflammatory drug which is commonly used to reduce vascular permeability and inhibit angiogenesis. The intravitreal injection of triamcinolone acetonide can make the effect last 2-3 weeks.<sup>[12]</sup> In this research, compared with the treatment with ranibizumab alone, the combination of ranibizumab and triamcinolone acetonide can much more obviously reduce CMT and remarkably improve visual acuity. It is indicated that the combined application of these two drugs have a positive and promotive effect on improving the visual function and reducing CMT in patients with wet AMD. Among the reasons for the good effect, it is probably because ranibizumab can reduce vascular permeability and

promote the absorption of internal exudation, and triamcinolone acetonide can enhance the barrier function of retina and relieve local inflammatory responses. Furthermore, the combined application can collaboratively improve the degree of macular degeneration by different ways.

IL-1 $\beta$  is one of important anti-inflammatory factors in IL-1 family, and it is mainly distributed in epithelial cells, endothelial cells or bone marrow cells. It can participate in local inflammatory responses.<sup>[13]</sup> Both IL-6 and IL-8 are important members of chemokine family, and they play a significant role in the inflammatory and the immune responses;<sup>[14]</sup> IL-2 is mainly generated by T cells, and it is an important cytokine for the interaction of lymphocytes and leukocytes. The increase in the level of IL-2 indicates the enhancement of leukocyte activity.<sup>[14]</sup> Past studies have indicated that the levels of aqueous fluid, PB inflammatory mediators and chemokines in patients with wet AMD keep in an elevated state, and they are involved in several processes such as macular degeneration, edema and repair of wet AMD.<sup>[15]</sup> Motohashi et al.<sup>[16]</sup> detected the inflammatory factors in the aqueous fluid from 13 cases of patients with wet AMD and found that the levels of IL-6 and IL-8 were obviously higher than those in patients with cataract. It is indicated that wet AMD is closely associated with inflammatory responses. In this research, intravitreal injection of ranibizumab in combination with triamcinolone acetonide was applied to the treatment of wet AMD. In the combination group, the levels of IL-1 $\beta$ , IL-6 and IL-8 in the serum were lower than those in the ranibizumab group, and the level of IL-2 was higher than that in the ranibizumab group. It is indicated that the combined application can effectively relieve the degree of inflammatory responses, and it may be associated with the anti-inflammatory effect of triamcinolone acetonide, which is similar to the research results from Yanhuan Zhao

et al.<sup>[17]</sup> In addition, there were no statistically significant differences in the incidence of bleeding, intraocular foreign body sensation and transient high IOP and the total incidence of complications between the two groups in this research. Furthermore, the symptoms of the complications are merely irritating and will be recovered automatically. It is indicated that the combined application of ranibizumab and triamcinolone acetonide is a safe and reliable method which will not increase the risk for the occurrence of the complications.

In conclusion, intravitreal injection of ranibizumab in combination with triamcinolone acetonide can effectively improve the visual function of wet AMD, reduce CMT, relieve inflammatory responses and show a safe and reliable performance that it doesn't cause the fluctuation of IOP. It provides a reference for the clinical treatment of wet AMD. However, the long-term clinical efficacy remains to be further studied.

## DECLARATION OF AUTHOR CONTRIBUTIONS

Xiaohong Sheng: participating in selecting the topic, designing, implementing the research, writing the thesis and revising the article according to the suggestions on revision from the editor. Xiangyang Xin: participating in selecting the topic, designing, making a statistical analysis and critically reviewing the thesis. Liming Wang: participating in selecting the topic, designing, implementing the research, collecting and analyzing the data. Yan Sun: participating in implementing the research, collecting and analyzing the data. Xiaohua Li: participating in making a statistical analysis, acquiring the research grants and so on.

## CONFLICTS OF INTEREST DISCLOSURE

The authors declare they have no conflicts of interest.

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