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An efficacy analysis of anti-vascular endothelial growth factor therapy for choroidal neovascularization secondary to multifocal choroiditis and comparison with wet age-related macular degeneration*

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Abstract: Objective: To evaluate the effect of anti-vascular endothelial growth factor (VEGF) on juxtafoveal choroidal neovascularization (CNV) secondary to multifocal choroiditis (MFC) and wet age-related macular degeneration (AMD). Methods: In this retrospective, comparative study, 20 unique eyes with CNV were divided into two groups: 10 patients affected by MFC and 10 patients diagnosed with wet AMD. They all received local intravitreal (IVT) injections of ranibizumab, with 6 months of follow-up. Retreatment injections were performed based on findings suggestive of active neovascularization. Results: Significant improvements were observed in the juxtafoveal CNV lesions, and average central macular thickness decreased in both groups following the anti-VEGF therapy (P<0.05). The average number of injections used in MFC patients was 1.6, while three injections on average were used in wet AMD patients (Z=−2.844, P=0.009). Best-corrected visual acuity was significantly improved in MFC patients after anti-VEGF therapy (P<0.05), and there was no significant difference in wet AMD patients between before anti-VEGF therapy and 6 months later (P>0.05). Conclusions: IVT ranibizumab resulted in good clinical outcomes for juxtafoveal CNV secondary to MFC and wet AMD, but the average number of injections used in MFC was fewer than that used in wet AMD over a 6-month observation period. Compared with the wet AMD group, visual acuity was obviously improved in the MFC group at 6 months.

Key words: Wet age-related macular degeneration (AMD); Multifocal choroiditis (MFC); Juxtafoveal choroidal neovascularization (CNV); Anti-vascular endothelial growth factor (VEGF) therapy
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1 Introduction

Multifocal choroiditis (MFC) is characterized by distinct spots of inflammation in the photoreceptor-retinal pigment epithelium complex. Choroidal neovascularization (CNV) is a well-known complication of MFC, often resulting in severe vision loss (Haen and Spaide, 2008; Thurau and Wildner, 2010). Many treatment options have been proposed for MFC-related CNV including steroids, immunosuppressants, photodynamic therapy, and surgical excision (Hochman et al., 1999; Gerth et al., 2006; Jutley et al., 2011; D'Ambrosio et al., 2014). However, these methods are not always sufficiently effective and some uncontrolled sub- or juxtafoveal CNVs may remain, significantly decreasing visual function, which is obviously an urgent and serious problem.

Wet age-related macular degeneration (AMD)—also called neovascular AMD—is characterized by CNV which may result in blurred vision in the center

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of the visual field, typically occurring in older people (Lim et al., 2012). It has been shown that anti-vascular endothelial growth factor (VEGF) therapy is successful in treating CNV for AMD (Cheung and Wong, 2011). Recently, Julián et al. (2011) and Iannetti et al. (2013) studied the administration of anti-VEGF agents for CNV related to MFC, with promising results. However, MFC is rare, so comparisons of the treatment outcomes between MFC and wet AMD following anti-VEGF therapy have rarely been reported.

In the present study, we aimed to examine the clinical therapeutic effect of anti-VEGF therapy on the outcomes of CNV secondary to MFC, and to compare this with its effect on wet AMD.

2 Methods

2.1 Patients with juxtafoveal CNV secondary to MFC and wet AMD

We selected 20 consecutive patients (12 males and 8 females) with juxtafoveal CNV who had attended the Eye Center at the Second Hospital Affiliated to Zhejiang University, Hangzhou, Zhejiang Province, China, between 2013 and 2015. The patients were grouped according to etiology: 10 were affected with MFC, while 10 had wet AMD. All patients were informed of the usage of the agent (ranibizumab) and its potential benefits and side effects. The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board.

Patients with juxtafoveal CNV secondary to MFC were recruited, and all underwent a complete ophthalmic examination. The inclusion criteria were as follows: a diagnosis of MFC, evidence of classic or occult CNV confirmed by fundus fluorescein angiography (FFA), and progressive vision loss related to the juxtafoveal neovascular manifestation after achieving strict control of intraocular inflammation with steroids and immunosuppressant treatments. The diagnosis of MFC was based on the presence of multiple chorioretinal lesions ranging in size from 50 to 350 μm, located in the posterior pole and/or the periphery zone, with the possible presence of vitreous cells and signs of anterior uveitis, as well as atrophy or peripapillary changes. The exclusion criteria were as follows: features and conditions such as AMD, pathological myopia, trauma, hereditary retinal disorders, any who previously have undergone photodynamic or anti-VEGF therapy.

Wet AMD was confirmed by FFA and optical coherence tomography (OCT). FFA was used to visualize the leakage of blood behind the macula and OCT was used to observe the neovascularization lesion. Those patients who had ever previously undergone photodynamic therapy or other retinal surgeries were excluded. All cases of MFC and wet AMD had identical investigations at baseline and follow-up visits.

2.2 Treatment approach

The decision to initiate intravitreal (IVT) injections was based on the progression of the CNV lesion and visual damage. All MFC patients had undergone strict control of intraocular inflammation—using steroids and immunosuppressant treatments—before IVT injections. However, the CNV was still present or had progressed, severely affecting visual function.

Patients in both groups received IVT injections of 0.5 mg/0.05 ml ranibizumab (Novartis Pharma Schweiz AG, Switzerland). Retreatment injections were carried out during the follow-up period when the OCT showed intra- and sub-retinal fluid and the FFA revealed leakage. The data were collected at several time points: before the initial treatment and 1, 2, 3, and 6 months after the first IVT injection. Antibiotic eye drops, such as levofloxacin, were used before and after the injections.

2.3 Outcome measurement

Slit lamp assessment, FFA, and Cirrus HD-OCT (Version 6.0; Carl Zeiss Meditec, Dublin, CA, USA) were performed for all patients before they received IVT ranibizumab and 1, 2, 3, and 6 months after the first IVT injection. Treatment success was defined as inactive CNV lesions (no leakage on FFA and shrinking on OCT). Macular edema was evaluated via OCT. Visual outcomes were evaluated using a logMAR chart, in order to determine whether visual function was decreased, maintained, or improved by treatment.

2.4 Statistical methods

All data were collected and analyzed using Statistical Package for the Social Sciences (SPSS) software, Version 18.0 (SPSS Inc., Chicago, IL, USA). They were examined for normality using the

Kolmogorov-Smirnov test, while the Mann-Whitney test was used to assess data of non-normal distribution. A paired *t*-test was used before and after anti-VEGF therapy, and an independent samples test was used for comparison between the two groups.

3 Results

3.1 CNV lesion changes before and after anti-VEGF therapy

FFA detected no fluorescein leakage or macular edema at the end of the follow-up period in any patients, and no systemic or ocular side effects were registered during anti-VEGF therapy.

Fig. 1 shows the clinical outcomes with regard to the right eye of a patient in the MFC group, before and 6 months after anti-VEGF therapy. Chorioretinal spots were visible on the color photography (Figs. 1a and 1b). Macular OCT demonstrated significant changes in the macular CNV lesion in a before-and-after comparison (Figs. 1c and 1d). FFA showed fluorescein leakage due to the CNV lesion before anti-VEGF therapy, but no leakage at the 6-month examination (Figs. 1e and 1f).

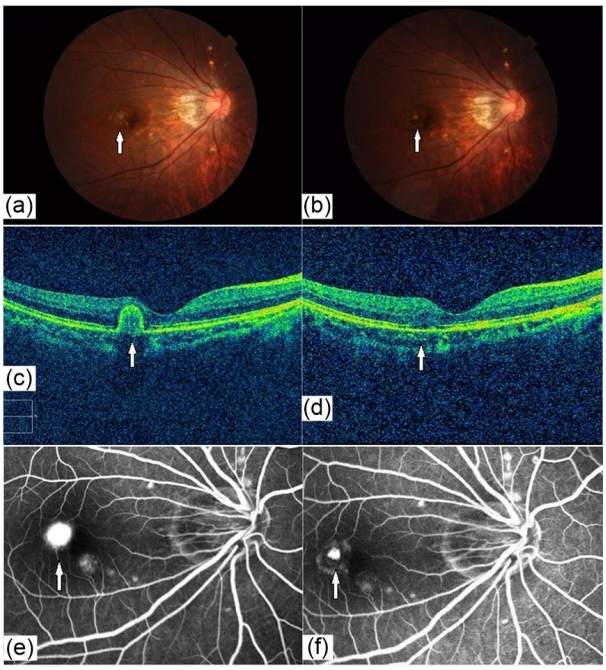

Fig. 1 Clinical outcomes before and six months after anti-VEGF therapy of the right eye of one MFC patient
(a, b) Color fundus photographs showing retinal inflammatory lesion (arrowheads) before and six months after the anti-VEGF therapy. (c, d) Spectral domain (SD)-OCT showing the CNV before anti-VEGF therapy disrupting the RPE and extending up to the level of the inner plexiform layer, and the lesion regressing six months after anti-VEGF therapy (arrowheads). (e, f) Fluorescein angiogram showing leakage from the CNV with fuzzy borders and staining of other atrophic lesions (arrowheads)

3.2 Comparison of injection number between MFC and wet AMD

In the MFC group, five patients received only one injection, two patients received two injections at monthly intervals, and the remaining three patients received three injections at monthly intervals. The mean number of anti-VEGF injections per eye in the MFC group was 1.6. In the wet AMD group, one patient received two injections at monthly intervals, one patient received four injections at monthly intervals, and the remaining eight patients received three injections at monthly intervals. There was a mean number of three anti-VEGF injections per eye in the wet AMD group. There was a statistically significant difference of injection number between the two groups (Z=−2.844, P=0.009). Table 1 summarizes the characteristics of the two groups of patients.

3.3 BCVA and CMT changes before and after anti-VEGF therapy

Best-corrected visual acuity (BCVA) and central macular thickness (CMT) showed a normal distribution before initiation of anti-VEGF therapy and 6 months after treatment (P>0.05), and are expressed as mean±standard deviation (Table 2). There was no statistically significant difference between the BCVA (logMAR) at baseline in the MFC group and between the wet AMD group (P=0.376), while a significant difference was observed between the BCVA (logMAR) in the MFC group and that in the wet AMD group, 6 months after anti-VEGF therapy (P<0.001). There was no statistically significant difference in CMT between the two groups, either at baseline or 6 months after anti-VEGF therapy (all P>0.05).

The BCVA and CMT baseline characteristics were compared between the initial evaluation and 6 months after anti-VEGF injections. As Table 2 shows, there was a significant difference in BCVA (logMAR) and CMT between baseline and 6 months after anti-VEGF therapy in the MFC group (t=5.063,

Table 1 Summary of data for patients with CNV secondary to MCF and wet AMD, treated with intravitreal anti-VEGF therapy

Case	Disease	Age (year)	Sex	Eye	Number of injections*
1	MCF	25	Male	Left	1
2	MCF	21	Female	Right	1
3	MCF	52	Male	Right	1
4	MCF	29	Female	Left	1
5	MCF	28	Female	Right	1
6	MCF	36	Male	Left	2
7	MCF	27	Female	Left	2
8	MCF	50	Male	Right	3
9	MCF	52	Female	Right	3
10	MCF	22	Female	Right	3
11	AMD	79	Male	Left	4
12	AMD	62	Female	Right	3
13	AMD	80	Male	Right	3
14	AMD	60	Male	Right	3
15	AMD	52	Male	Right	2
16	AMD	72	Female	Right	3
17	AMD	58	Male	Right	3
18	AMD	63	Male	Right	3
19	AMD	77	Male	Right	3
20	AMD	57	Male	Right	3

MCF: multifocal choroiditis; AMD: macular degeneration. * Mann-Whitney text (comparison between groups MCF and AMD): $Z=-2.844$, $P=0.009$

Table 2 BCVA and CMT before and six months after anti-VEGF in two groups

Group	BCVA (logMAR)		CMT (μmol/L)	
	Baseline	Six months later	Baseline	Six months later
MCF	0.58±0.39	0.13±0.19	307.90±113.42	239.10±56.13
AMD	0.73±0.32	0.68±0.25	305.10±115.80	273.90±69.66

BCVA: best-corrected visual acuity; CMT: central macular thickness; MCF: multifocal choroiditis; AMD: macular degeneration. Data are expressed as mean±standard deviation ($n=10$)

$P=0.001$ and $t=7.314$, $P=0.046$, respectively). Moreover, a significant difference in CMT between baseline and 6 months after anti-VEGF therapy was observed in the wet AMD group ($t=4.079$, $P=0.003$). However, no statistically significant difference in BCVA was found in the wet AMD group between baseline and 6 months after anti-VEGF therapy ($t=0.400$, $P=0.698$).

4 Discussion

MFC is a chronic disease with a high risk of CNV (Kuo and Cunningham, 2000), a common cause of severe vision loss, and steroids and immunosuppressants are the traditional treatments for this disease. However, in all of our study patients, CNV secondary to MFC still developed and caused vision loss, even after strict control of intraocular inflammation had been achieved using steroids and immunosuppressant treatments. This phenomenon was documented by Dunlop et al. (1998), who reported that the possible causes were chronic perivascular B-cell lymphocytic infiltration and breakage of Bruch's membrane.

Perentes et al. (2002) reported that inflammation may cause the release of chemokines that induce angiogenesis. Further, as mentioned in Table 3, photodynamic therapy could not improve visual acuity (VA) in all patients, but it remained stable. Shimada et al. (2008) identified VEGF overexpression in samples of active CNV obtained after surgical excision in MFC patients. Therefore, it appears that anti-neovasculature therapy is theoretically required, as conventional therapy does not adequately prevent the development of CNV in some MFC cases.

VEGF is a type of growth factor specific for endothelial cells and a regulator of angiogenesis. High levels of VEGF expression are involved in the ocular neovascularization process; therefore, blocking these potent factors may be a new treatment for ocular neovascular diseases (Starita et al., 2007). VEGF inhibition was initially approved by the United States Food and Drug Administration (FDA) for the treatment of CNV due to AMD. The role of VEGF inhibition in diabetic retinopathy, wet AMD, and retinal vein occlusions has since been widely studied. However, relatively few studies have examined inflammatory CNV (Gulati et al., 2011; Rouvas et al., 2011), and evidence-based guidelines on anti-VEGF treatment for MFC are still lacking.

The results of the present study are encouraging, as the CNV lesions in all ten MFC patients developed continuously into scars and no active lesions were detected at the final examination. Furthermore, all patients showed a significant improvement in BCVA and their OCT macular thickness measurements were significantly improved compared to baseline values in

Table 3 Comparison between present work and previous ones conducted by other treatment options for inflammatory CNV

Treatment	Disease	Year	Country	Improvement in BCVA (% of cases)	Reference
Anti-VEGF	MCF	2017	China	7/7	Present study
Systemic oral prednisolone	PIC, MIC	1998	UK	7/10	Flaxel et al., 1998
Surgical removal	Ocular histoplasmosis syndrome	1994	USA	56/67	Thomas et al., 1994
Photodynamic therapy	MCF	2002	USA	4/7	Spaide et al., 2002

MCF: multifocal choroiditis; PIC: punctate inner choroidopathy; MIC: multifocal inner choroiditis

the MFC group. Previous studies have also used anti-VEGF therapy for certain cases. For example, Dardabounis and Panos (2013) reported the successful treatment of peripapillary CNV in a 54-year-old woman with MFC, and Fine et al. (2009) reported that anti-VEGF agents were effective in improving VA over 6 months in six patients with MFC-associated CNV. Consequently, the use of anti-VEGF therapy in CNV due to MFC may prove to be a beneficial treatment.

The average number of injections in MFC patients in our study was 1.6, which was fewer than that used in wet AMD, which was similar to cases reporting treatment for wet AMD (Alexandru and Alexandra, 2016). The possible reasons for this are as follows. First, the CNV in these MFC patients was driven by two factors—previous inflammatory status and VEGF signaling. Kwak et al. (2000) pointed out that VEGF signaling plays a critical role in the development of CNV. It has been shown that VEGF and extravascular inflammatory components are present in neovascular membranes (Tsutsumi-Miyahara et al., 2004). All the patients in the present study had already achieved strict control of intraocular inflammation with steroids and immunosuppressants before the administration of ranibizumab, and none had cellular activity in the anterior chamber or in the vitreous humor, so the extravascular inflammatory components of the neovascular membrane were controlled. Ranibizumab was used to inhibit VEGF signaling. Second, the median age of our patients was 36 years, while AMD patients are usually aged over 50 years. Younger people are much more likely than older people to recover vision.

As an important cause of vision loss among people younger than 50 years, untreated inflammatory CNV can cause a rapid decline, and the prognosis is poor in this population (Miller and Singerman, 2006). Our study showed good clinical results for CNV secondary to MFC, highlighting the potential utility of anti-VEGF therapy in treating inflammatory CNV.

Compliance with ethics guidelines

Lei FENG, Jiang-hua HU, Jie CHEN, and Xin XIE declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

References

Alexandru MR, Alexandra NM, 2016. Wet age related macular degeneration management and follow-up. *Rom J Ophthalmol*, 60(1):9-13.

Cheung CM, Wong TY, 2011. Ranibizumab and bevacizumab for AMD. *N Engl J Med*, 365(23):2237. https://doi.org/10.1056/NEJMc1107895

D'Ambrosio E, Tortorella P, Iannetti L, 2014. Management of uveitis-related choroidal neovascularization: from the pathogenesis to the therapy. *J Ophthalmol*, 2014:450428. https://doi.org/10.1155/2014/450428

Dardabounis D, Panos GD, 2013. Intravitreal ranibizumab in choroidal neovascularisation due to multifocal choroiditis and panuveitis syndrome. *BMJ Case Rep*, 2013: bcr2013009572 https://doi.org/10.1136/bcr-2013-009572

Dunlop AA, Cree IA, Hague S, et al., 1998. Multifocal choroiditis: clinicopathologic correlation. *Arch Ophthalmol*, 116(6):801-803. https://doi.org/10.1001/archopht.116.6.801

Fine HF, Zhitomirsky I, Freund KB, et al., 2009. Bevacizumab (avastin) and ranibizumab (lucentis) for choroidal neovascularization in multifocal choroiditis. *Retina*, 29(1): 8-12. https://doi.org/10.1097/IAE.0b013e318187aff9

Flaxel CJ, Owens SL, Mulholland B, et al., 1998. The use of corticosteroids for choroidal neovascularisation in young patients. *Eye*, 12:266-272.

Gerth C, Spital G, Lommatzsch A, et al., 2006. Photodynamic therapy for choroidal neovascularization in patients with multifocal choroiditis and panuveitis. *Eur J Ophthalmol*,

16(1):111-118.
https://doi.org/10.1177/112067210601600118

Gulati N, Forooghian F, Lieberman R, et al., 2011. Vascular endothelial growth factor inhibition in uveitis: a systematic review. *Br J Ophthalmol*, 95(2):162-165.
https://doi.org/10.1136/bjo.2009.177279

Haen SP, Spaide RF, 2008. Fundus autofluorescence in multifocal choroiditis and panuveitis. *Am J Ophthalmol*, 145(5):847-853.
https://doi.org/10.1016/j.ajo.2008.01.008

Hochman MA, Weiter JJ, Fleckner MR, et al., 1999. Surgical management of choroidal neovascular membranes. *Int Ophthalmol Clin*, 39:303-315.

Iannetti L, Paroli MP, Fabiani C, et al., 2013. Effects of intravitreal bevacizumab on inflammatory choroidal neovascular membrane. *Eur J Ophthalmol*, 23(1):114-118.
https://doi.org/10.5301/ejo.5000192

Julián K, Terrada C, Fardeau C, et al., 2011. Intravitreal bevacizumab as first local treatment for uveitis-related choroidal neovascularization: long-term results. *Acta Ophthalmol*, 89(2):179-184.
https://doi.org/10.1111/j.1755-3768.2010. 02046.x

Jutley G, Jutley G, Tah V, et al., 2011. Treating peripapillary choroidal neovascular membranes: a review of the evidence. *Eye*, 25(6):675-681.
https://doi.org/10.1038/eye.2011.24

Kuo IC, Cunningham ET, 2000. Ocular neovascularization in patients with uveitis. *Int Ophthalmol Clin*, 40(2):111-126.
https://doi.org/10.1097/00004397-200004000-00009

Kwak N, Okamoto N, Wood JM, et al., 2000. VEGF is major stimulator in model of choroidal neovascularization. *Invest Ophthalmol Vis Sci*, 41(10):3158-3164.

Lim LS, Mitchell P, Seddon JM, et al., 2012. Age-related macular degeneration. *Lancet*, 379(9827):1728-1738.
https://doi.org/10.1016/S0140-6736(12)60282-7

Miller DG, Singerman LJ, 2006. Vision loss in younger patients: a review of choroidal neovascularization. *Optom Vis Sci*, 83(5):316-325.
https://doi.org/10.1097/01.opx.0000216019.88256.eb

Perentes Y, Chan CC, Bovey E, et al., 2002. Massive vascular endothelium growth factor (VEGF) expression in Eales' disease. *Klin Monbl Augenheilkd*, 219(4):311-314.
https://doi.org/10.1055/s-2002-30662

Rouvas A, Petrou P, Douvali M, et al., 2011. Intravitreal ranibizumab for the treatment of inflammatory choroidal neovascularization. *Retina*, 31:871-879.

Shimada H, Yuzawa M, Hirose T, et al., 2008. Pathological findings of multifocal choroiditis with panuveitis and punctate inner choroidopathy. *Jpn J Ophthalmol*, 52(4):282-288.
https://doi.org/10.1007/s10384-008-0566-2

Spaide RF, Freund KB, Slakter J, et al., 2002. Treatment of subfoveal choroidal neovascularization associated with multifocal choroiditis and panuveitis with photodynamic therapy. *Retina*, 22(5):545-554.
https://doi.org/10.1097/00006982-200210000-00003

Starita C, Patel M, Katz B, et al., 2007. Vascular endothelial growth factor and the potential therapeutic use of pegaptanib (macugen) in diabetic retinopathy. *Diabetic Retinopathy*, 39:122-148.
https://doi.org/10.1159/000098504

Thomas MA, Dickinson JD, Melberg NS, et al., 1994. Visual results after surgical removal of subfoveal choroidal neovascular membranes. *Ophthalmology*, 101:1384-1396.
https://doi.org/10.1016/S0161-6420(94)31172-9

Thurau S, Wildner G, 2010. Choroidtis. *Ophthalmologe*, 107:79-91 (in German).
https://doi.org/10.1007/s00347-009-2116-9

Tsutsumi-Miyahara C, Sonoda KH, Egashira K, et al., 2004. The relative contributions of each subset of ocular infiltrated cells in experimental choroidal neovascularisation. *Br J Ophthalmol*, 88(9):1217-1222.

中文概要

题　目：抗 VEGF 药物在多灶性脉络膜炎和湿性老年性黄斑变性中的疗效观察和比较

目　的：比较抗血管内皮生长因子（VEGF）药物对多灶性脉络膜炎（MFC）和湿性老年性黄斑变性（AMD）的疗效。

创新点：MFC 是一种特发性脉络膜视网膜病变，容易并发多灶性脉络膜新生血管，治疗棘手，易复发。目前有个别病例报道证明抗 VEGF 对其新生血管的治疗有效果，但是缺少更多的数据比较。本文将抗 VEGF 药物对 MFC 和 AMD 的疗效进行对比，以了解其在不同疾病中的疗效。

方　法：收集 MFC 并发络膜新生血管和 AMD 并发络膜新生血管患者各 10 名，予以玻璃体腔注射抗 VEGF 药物，跟踪随访患者 6 个月的视力变化、新生血管大小、黄斑水肿情况。随访期间采用眼底血管造影以及光学相干断层扫描进行监测，如发现有活动性脉络膜新生血管，予以再次注射。

结　论：抗 VEGF 药物对 MFC 并发的脉络膜新生血管有良好的治疗效果，注射次数少于湿性 AMD 并发的新生血管治疗，且视力恢复情况也较其明显。

关键词：湿性老年性黄斑变性（AMD）；多灶性脉络膜炎（MFC）；血管内皮生长因子（VEGF）