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Observation of intravitreal injections of ranibizumab for myopic choroidal neovascularization in Chinese patients

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玻璃体内注射雷珠单抗治疗病理性近视脉络膜新生血管

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摘要

目的:评价玻璃体内注射雷珠单抗治疗病理性近视脉络膜新生血管的视力和解剖结果。

方法:本文为回顾性病例性研究。本研究纳入35例患眼。所有患眼依据持续或复发性脉络膜新生血管(CNV)进行一次初始计量为0.5mg的雷珠单抗玻璃体内注射治疗。最佳矫正视力(BCVA),荧光素眼底血管造影(FFA)显示的CNV,光学相干断层扫描(OCT)显示的中央视网膜厚度(CRT),治疗总次数和并发症都将作为评估指标。

结果:平均随访时间20mo(范围:16~24mo),28例(80%)患眼随访超过22mo。治疗后基线平均最佳矫正视力(BCVA) logMAR 0.74±0.23显著提高到BCVA logMAR 0.49±0.31(P<0.001, Wilcoxon秩检验)。末次随访,35例患眼中21例(60%)显示BCVA提高2行或2行以上,13例(37%)BCVA没有变化,1例(3%)BCVA下降2行以上。平均中央视网膜厚度(CRT)从297±72μm下降到228±61μm (P<0.001, 配对t检验)。随访期间,平均注射次数是3.2次(SD, 0.94;范围1~7次)。治疗后未发现并发症。

结论:本研究的结果显示雷珠单抗玻璃体内注射治疗病理性近视CNV是安全和有效的。

关键词:黄斑变性;病理性近视;血管内皮生长因子

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Abstract

• AIM: To evaluate the visual and anatomic outcomes of intravitreal ranibizumab injections for myopic choroidal neovascularization (mCNV) in Chinese patients.

• METHODS: This study is a retrospective case. Thirty-five patients treated for mCNV were included in this study. Their eyes were treated with a single intravitreal injection of 0.5 mg ranibizumab following a pro re nata (PRN) regimen indicated by persistent or recurrent CNV. Best corrected visual acuity (BCVA), CNV findings on fundus fluorescent angiography (FFA), central retinal thickness (CRT) on optical coherence tomography (OCT), total number of treatments, and complications were evaluated.

• RESULTS: The mean follow-up duration was 20mo (range 16-24mo). Twenty-eight patients (80%) were followed up for more 22mo. The mean baseline BCVA was 0.74 logarithm of the minimum angle of resolution (logMAR) [standard deviation (SD) 0.23] and improved significantly to 0.49 logMAR (SD 0.31) (P<0.001, Wilcoxon signed-rank test) after treatment. At the final months of follow-up, 21 of the 35 eyes (60%) showed an improvement of 2 lines or more in BCVA, 13 eyes (37%) remained unchanged, and 1 eye (3%) had a deterioration of 2 lines or more. Mean CRT decreased from 297 μm (SD, 72) at baseline to 228 μm (SD, 61) at the final follow-up (P<0.001, paired t-test). During follow-up, the mean number of repeat injections was 3.2 (SD, 0.94; range, 1-7 injections). No drug-related complications were observed after treatment.

• CONCLUSION: The long-term outcomes observed in this study suggest that intravitreal ranibizumab is safe and effective for treating mCNV.

• KEYWORDS: macular degeneration; myopia; vascular endothelial growth factor

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INTRODUCTION

Pathological myopia (PM) is the leading cause of severe visual loss among people in many countries[1,2]. High myopia is especially common in Asian populations, with incidence rates of 9%-21%[3,4] compared with 2%-4% in

Caucasians[5-7]. Choroidal neovascularization (CNV) caused by PM, known as myopic CNV (mCNV), is a serious vision-threatening condition in these patients. Among secondary causes of CNV, myopia is the most common, accounting for 62% of all CNV cases in patients less than 50 years of age [8]. The natural progression of the disease and visual prognosis in mCNV are generally poor without treatment, and thus, severe visual loss significantly impacts the patients' quality of life[9]. Although there is a lack of evidence based on randomized controlled trials, photodynamic therapy (PDT) with verteporfin has been shown to be effective and is recommended as the first-line treatment for patients with mCNV. However, the long-term outcome of PDT is not favorable, as patients generally show no improvement in mean visual acuity following treatment, and the beneficial effect of PDT in preventing visual loss was found to be no longer significant at 2y[10,11]. Moreover, the high cost of PDT limits its use, particularly in developing countries.

An alternative treatment for patients with CNV is anti-vascular endothelial growth factor (VEGF) therapy, including bevacizumab (Avastin, Genentech, South San Francisco, CA, USA) and ranibizumab (Lucentis, Novartis, Basel, Switzerland). Most of the studies investigating these treatments have demonstrated significant mean visual improvement after anti-VEGF therapy, and the beneficial effects were maintained at 12mo. In contrast with these short-term results, the longer-term results were more variable, with studies reporting that the initial visual gain may no longer be significant at 2y[12,13]. To further assess the efficacy of anti-VEGF therapy for mCNV, we evaluated the long-term outcomes with the use of intravitreal ranibizumab as the primary treatment for mCNV in Chinese patients.

SUBJECTS AND METHODS

Subjects This study was designed as a retrospective, consecutive, noncomparative, interventional study aimed at investigating the visual and anatomic outcomes as well as the safety of intravitreal ranibizumab in patients with mCNV. This study included 35 patients (35 eyes) with mCNV who were administered intravitreal injection of ranibizumab at the Department of Ophthalmology of the First Hospital of China Medical University from July 2012 to January 2013. The inclusion criteria included follow-up of at least 16mo, myopia with a spherical equivalent refractive error of -6 D or more, subfoveal CNV location, best corrected visual acuity (BCVA) of 20/800 or better, and evidence of CNV leakage on fluorescein angiography (FA). Exclusion criteria included juxtafoveal or extrafoveal CNV; prior treatment of CNV including PDT or thermal laser photocoagulation; and features suggesting CNV was secondary to age-related macular degeneration (AMD) or other causes such as trauma, choroiditis, angioid streaks, and hereditary diseases in the study eye or fellow eye. Informed consent was obtained from all patients before treatment, and the study was approved by an Institutional Review Board and performed with adherence to the tenets of the Declaration of Helsinki. All eyes underwent complete ophthalmologic evaluation at baseline, which included BCVA testing using a standard Snellen chart, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement, indirect ophthalmoscopy, FA, indocyanine green angiography (ICGA), and optical coherence tomography (OCT) (Stratus OCT; Carl Zeiss Meditec, Dubin, CA, USA). Central retinal thickness (CRT; thickness of the 1-mm central retina) was measured by the fast macular scan protocol of OCT.

Methods Each patient received an intravitreal injection of 0.5 mg ranibizumab (0.05 mL) at baseline. All injections were given under sterile conditions in the operating room. Povidone-iodine solution was used to clean the eyelids, and a lid speculum was inserted. Next, topical anesthesia was applied, and the conjunctiva was irrigated with 5% povidone-iodine. A 30-gauge needle was inserted through the pars plana, and 0.05 mL ranibizumab was injected into the vitreous cavity. Follow-up examinations were performed 1d, 1wk, and 1mo after the injection and then monthly thereafter for at least 16mo. BCVA testing, slit-lamp examination, IOP measurement, indirect ophthalmoscopy, and OCT were performed at each visit. FA and ICGA were recorded at the initial visit and three months follow-up visit for each injection. Time-domain OCT was also performed in every patients to evaluate the treatment response and to guide retreatment in cases of recurrence. Additional reinjections were given at least 4wk after the previous injection according to the following criteria: 1) self-reported significant central visual acuity loss; 2) new macular hemorrhage; 3) recurrence of any subretinal fluid of cystic maculopathy on OCT in a previously dry macula; and 4) persistent intraretinal or subretinal fluid on OCT. The primary outcome was improved (≥2 lines), stabilized (within 1 line), or deteriorated (≥2 lines) vision at the final follow-up. The main outcome measures included changes in the mean BCVA and CRT from baseline to the final follow-up, angiographic and anatomic changes, number of treatments, and ocular and systemic safety.

Statistical Analysis Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 17.0.1; SPSS Inc, Chicago, IL, USA). Snellen visual acuity was converted to the logarithm of the minimum angle of resolution (logMAR) equivalent for statistical analysis. Data are expressed as mean ± standard deviation (SD). Normally distributed continuous variables were compared using the paired t test. The Wilcoxon signed-rank test was used to compare data that were not normally distributed. The association between the change in CRT and BCVA outcomes was assessed using the Pearson correlation analysis. A P value of <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics Thirty-five consecutive patients (35 eyes) with mCNV were included in this study. All the enrolled patients were Chinese; 24 were female (69%) and

11 were male (31%). Twenty eyes (57%) were the left eye. The mean patient age at the start of the study was 53.5y (range 26-69y). The mean spherical equivalent refractive error was -9.8±3.1 D). The duration of symptoms varied from 7d to 2y (<3mo, 27 eyes, 77%; 3mo to 1y, 6 eyes, 17%; >1y, 2 eyes, 6%). The Snellen BCVA at baseline ranged from 20/200 to 20/25, with a median of 20/100. The mean logMAR BCVA before treatment was 0.74±0.23 (20/110 in Snellen equivalent). The mean CRT at baseline was 297±72 μm, as measured by OCT. The mean follow-up duration was 20mo (range 16-24mo).

Visual Outcomes Mean BCVA improved from 0.74 (SD, 0.23) logMAR at baseline to 0.49 (SD, 0.31) logMAR at the final follow-up. The mean improvement in logMAR BCVA at the final follow-up was 2.5 lines, and the improvement from baseline remained statistically significant (Wilcoxon signed-rank test, $P<0.001$, Figure 1). At the final follow-up, 21 of the 35 eyes (60%) showed an improvement of 2 lines or more in BCVA, 13 eyes (37%) remained unchanged, and 1 eye (3%) had a deterioration of 2 lines or more.

Changes in OCT and Angiography Mean CRT decreased from 297μm (SD, 72) at baseline to 228 μm (SD, 61) at the final follow-up ($P<0.001$, paired t-test, Figure 2). There was a statistically significant correlation between the improvement in mean BCVA (logMAR) and the decrease in mean CRT at the final follow-up (Pearson correlation analysis; $r=0.54$, $P<0.001$). At the final follow-up, all 35 eyes were in the cicatricial stage of CNV. FA showed absence of leakage from CNV lesions and no intraretinal edema, subretinal fluid (SRF), or retinal pigment epithelial detachment (PED) was indicated by OCT.

Number of Treatments During follow-up, 26 eyes (74%) needed reinjection, and the mean number of repeat injections was 3.2 (SD, 0.94; range 1-7 injections). At 6mo after the initial injection, only 5 eyes (14%) needed reinjection.

Complications None of the patients developed any ocular (endophthalmitis, retinal detachment, or uveitis) or nonocular (thromboembolic event or systemic hypertension) complications related to intravitreal ranibizumab.

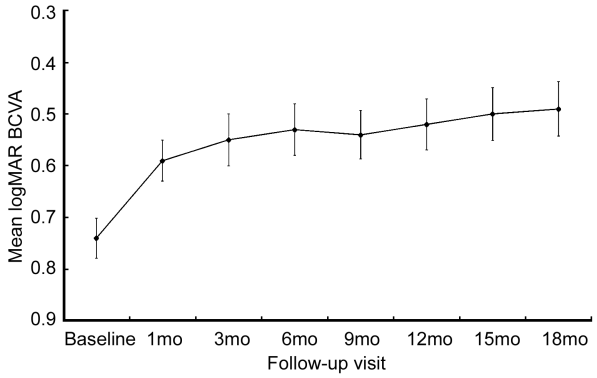

Figure 1 Mean BCVA (logMAR) in mCNV eyes treated with ranibizumab at each follow-up visit.

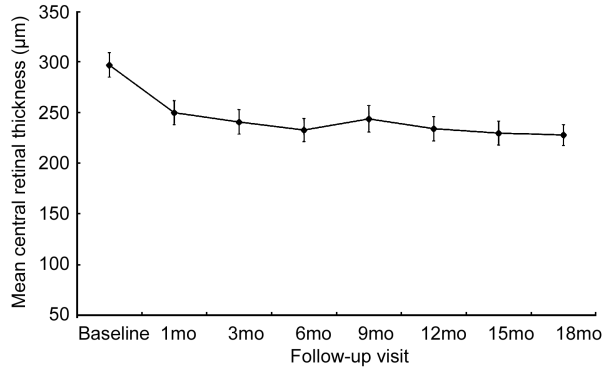

Figure 2 Mean CRT in mCNV eyes treated with ranibizumab at each follow-up visit.

DISCUSSION

Eyes with pathologic myopia are known to have extremely elongated axial length, chorioretinal degeneration, and lacquer cracks, and CNV is an important cause of visual loss in these eyes. Although self-limiting, CNV can cause subretinal hemorrhage, exudation, fibrosis, and atrophic scars, leading to permanent visual loss[14].

VEGF is a potent permeability factor and growth factor involved in the development of CNV, and VEGF inhibitors represent a relatively new treatment for CNV. Ranibizumab, an anti-angiogenic medication, can block the effects of VEGF. It has been approved and widely used as the primary treatment for CNV secondary to AMD[15]. On the basis of its theoretical and therapeutic effects on CNV, ranibizumab may also be used to effectively treat CNV secondary to pathologic myopia. In the past few years, intravitreal ranibizumab has gained increasing popularity in the treatment of mCNV, as multiple studies have shown that anti-VEGF agents are effective in improving the vision of patients with mCNV[10,16-24]. However, many previous studies have included both treatment of naive cases and previously treated eyes, as well as subfoveal and nonsubfoveal CNV in the series, making comparisons of the results more difficult. The main strengths of our current study included the relatively long follow-up of more than 1y and the homogeneity of cases with treatment of only naive subfoveal mCNV.

PDT once showed favorable outcomes at 1-year follow-up in a randomized, double-masked, placebo-controlled study of verteporfin combined with PDT (the VIP Study)[25]. However, the long-term efficacy was not statistically significant according to a 2-year report published in 2003[26]. Wolf *et al*[27] also evaluated the use of anti-VEGF therapy with intravitreal ranibizumab, PDT, and combined anti-VEGF with PDT in the treatment of mCNV. The results at 12mo showed that anti-VEGF therapy improved and sustained BCVA more effectively compared with both the combination and PDT groups. Because patients with pathologic myopia frequently have chorioretinal atrophy associated with mCNV, it may not be advisable to perform PDT in these patients, as the PDT can further exacerbate chorioretinal damage in these patients by damaging the already comprised choriocapillaris.

In the present study, we showed a statistically significant improvement in mean logMAR BCVA from 0.74 to 0.49 and a

Table 1 Comparison of the outcome in different series on intravitreal ranibizumab for myopic choroidal neovascularization

Study design	Present study Retrospective	Mones *et al*[24] (2009) Retrospective	Iacono *et al*[28] (2012) Retrospective	Cha *et al*[29] (2014) Retrospective
No. of eyes	35	23	23	23
Follow-up, range (mo)	20 (16-24)	12	18	12 (22.87±9.10)
Location of CNV	SF	SF, JF	SF	SF, JF
Previous Therapy	No	N/A	No	No
Schedule	1+PRN	1+PRN	1+PRN	1+PRN
Mean number of IVR	3.2±0.94	1.52	2.56±1.61	2.43±1.04
VA(LogMAR/Letters)	0.74±0.23	N/A	0.60±0.29	0.63±0.30
Mean final VA (LogMAR/Letters)	0.49±0.31	62.57±19.27	0.40±0.38	0.39±0.42
Mean change in VA	+2.5 lines	+9.53 letters	+1.8±0.27 lines	N/A
Improved[1]	21/35 (60%)	8/23 (34.7%)	7/23 (30%)	17/23 (74%)
Stable[2]	13/35 (37%)	12/23 (52.2%)	15/23 (65%)	5/23 (22%)
Decreased[3]	1/35 (3%)	3/23 (13.1%)	1/23 (5%)	1/23 (4%)

SF: Subfoveal; JF: Juxtafoveal; N/A: Not available; IVR: Intravitreal ranibizumab; VA: Visual acuity; 1+PRN: Single loading dose followed by pro re nata treatment; LogMAR: Logarithm of the minimum angle of resolution. [1]Present study and Cha's study VA≥2 lines increase; Mones's study and Iacono's study VA≥3 lines increase; [2]Present study and Cha's study +1≥VA≥-1 lines; Mones's study and Iacono's study +2≥VA≥-2 lines; [3]Present study and Cha's study VA≥2 lines decrease; Mones's study and Iacono's study VA≥3 lines decrease.

mean improvement of 2.5 lines in BCVA from baseline at the final follow-up. Consistent with this improvement in BCVA, OCT revealed a marked decrease in retinal thickness from 297μm (SD, 72) at baseline to 228μm (SD, 61) at the final follow-up (P<0.001, paired t-test, Figure 2). There was a statistically significant correlation between the improvement in mean BCVA (logMAR) and the decrease in mean CRT at the final follow-up (Pearson correlation analysis; r = 0.54, P < 0.001). The mean number of treatments was 3.2 injections (range 1-7) per eye during the follow-up period, resulting in all lesions converting to the cicatricial stage.

The appropriate strategy for administering intravitreal ranibizumab injections in the treatment of CNV, including the number and frequency of injections, remains uncertain to date. Three monthly injections (3+PRN) more effectively improved the patients' vision during early stage of treatment. Lai *et al*[21] reported a series of 16 eyes with 3+PRN for mCNV. The mean improvement at 12mo was 3.0 lines, and 12 (75.0%) eyes had improvement of 2 or more lines. Fifteen (93.75%) eyes exhibited angiographic closure at 3mo, and one eye (6.25%) required further treatment because of persistent leakage at 3mo. Two (12.5%) patients experienced recurrence of CNV and required retreatment between 3 and 9mo. Wu and Kung[23] reviewed 25 eyes with mCNV with a follow-up duration of 12mo. At 12mo, the mean improvement in vision was 2.88 lines, and 20 eyes (80%) showed a gain of at least 1 line after treatment. The average number of injections was 3.44. However, the 1+PRN group required fewer injections than the 3+PRN group within 12mo. In a study by Mones *et al*[24], 23 eyes with mCNV required subsequent intravitreal ranibizumab as needed after the first injection (1+PRN). At the 12-month follow-up, the mean BCVA was improved by 9.53 letters. In all, vision in 69% of patients increased by least 1 line, and that in 34.7% of the patients increased by 3 or more lines. Patients received an average of 1.52 injections. In another study of 23 eyes by Lacono *et al*[28], at the 18-month examination, BCVA (logMAR) improved from 0.60±0.29 to 0.40±0.38 after treatment, and a significant improvement of 1.8 lines compared with baseline were noticed. A 3-line gain or higher was noted in 30% of eyes. The number of injections was 2.5. Cha *et al*[29] reported that the treatment of 23 mCNV over an 12-month follow-up. BCVA (logMAR) improved from 0.63±0.30 to 0.39±0.42 at 12mo after treatment, and BCVA improved by 2 or more lines in 17 of 23 eyes (74%). Patients received an average of 2.43±1.04 injections (Table 1). Therefore, it is still unknown whether the visual outcome and required number of injections will show any differences with a longer period of follow-up.

In terms of complications, neither retinal breaking nor retinal detachment was noted in our study. In addition, none of the patients had any other systemic or ocular side effects. Moreover, the total numbers of treatments during the study period did not appear to be higher than those in other studies, and greater than 80% of eyes treated with single loading dose gained at least 1 line of visual improvement after the study period. Accordingly, we consider that one single injection followed by PRN might be a reasonable choice for mCNV.

The main limitations of our study include its retrospective nature and the lack of an untreated control group for comparison. The symptoms persisted for a slightly longer duration and a trend of declining baseline visual acuity was observed. Future long-term, prospective, randomized trials are needed to compare the safety and outcomes for different dosing regimens of intravitreal ranibizumab.

REFERENCES

1 Iwase A, Araie M, Tomidokoro A, Yamamoto T, Shimizu H, Kitazawa Y, Tajimi Study Group. Prevalence and causes of low vision and blindness in a Japanese adult population: the Tajimi Study. *Ophthalmology* 2006;113(8):1354-1362

2 Cotter SA, Varma R, Ying-Lai M, Azen Sp, Klein R. Los Angeles Latino Eye Study Group. Causes of low vision and blindness in adult Latinos: the Los Angeles Latino Eye Study. *Ophthalmology* 2006;113(9):1574-1582

3 Lin LL, Shih YF, Hsiao CK, Chen CJ. Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. *Ann Acad Med Singapore* 2004;33(1):27-33

4 Wong TY, Foster PJ, Hee J, Ng TP, Tielsch JM, Chew SJ, Johnson GJ, Seah SK. Prevalence and risk factors for refractive errors in adult Chinese in Singapore. *Invest Ophthalmol Vis Sci* 2000;41(9):2486-2494

5 Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7(4):403-422

6 Wang Q, Klein BE, Klein R, Moss SE. Refractive status in the Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci* 1994;35(13):4344-4347

7 Attebo K, Ivers RQ, Mitchell P. Refractive errors in an older population: the Blue Mountains Eye Study. *Ophthalmology* 1999;106(6):1066-1072

8 Cohen SY, Laroche A, Leguen Y, Soubrane G, Coscas GJ. Etiology of choroidal neovascularization in young patients. *Ophthalmology* 1996;103(8):1241-1244

9 Yoshida T, Ohno-Mataui K, Yasuzumi K, Kojima A, Shimada N, Futaqami S, Tokoro T, Mochizuki M. Myopic choroidal neovascularization: a 10-year follow-up. *Ophthalmology* 2003;110(7):1297-1305

10 Chan WM, Ohji M, Lai TY, Liu DT, Tano Y, Lam DS. Choroidal neovascularisation in pathological myopia: an update in management. *Br J Ophthalmol* 2005;89(11):1522-1528

11 Coutinho AM, Silva RM, Nunes SG, Cachuio ML, Figueira JP, Murta JN. Photodynamic therapy in highly myopic eyes with choroidal neovascularization: 5 years of follow-up. *Retina* 2011;31(6):1089-1094

12 Ikuno Y, Nagai Y, Matsuda S, Arisawa A, Sho K, Oshita T, Takahashi K, Uchihori Y, Gomi F. Two-year visual results for older Asian women treated with photodynamic therapy or bevacizumab for myopic choroidal neovascularization. *Am J Ophthalmol* 2010;149(1):140-146

13 Ruiz-Moreno JM, Montero JA. Intravitreal bevacizumab to treat myopic choroidal neovascularization: 2-year outcome. *Graefes Arch Clin Exp Ophthalmol* 2010;248(7):937-941

14 Avila MP, Weiter JJ, Jalkh AE, Trempe CL, Preutt RC, Schepens CL. Natural history of choroidal neovascularization in degenerative myopia. *Ophthalmology* 1984;91(12):1573-1581

15 Ciulla TA, Rosenfeld PJ, Ciulla TA, Rosenfeld PJ, Antivascular endothelial growth factor therapy for neovascular age-related macular degeneration. *Curr Opin Ophthalmol* 2009;20(3):158-165

16 Gharbiya M, Giustolisi R, Allievi F, Fantozzi N, Mazzeo L, Scavella V, Gabrieli CB. Choroidal neovascularization in pathologic myopia: intravitreal Ranibizumab versus bevacizumab: a randomized controlled trial. *Am J Ophthalmol* 2010;149(3):458-464

17 Silva RM, Ruiz-Moreno JM, Nascimento J, Carneiro A, Rosa P, Barbosaa A, Carvalheira F, Abreu JR, Cunha-Vaz JG. Short-term efficacy and safety of intravitreal Ranibizumab for myopic choroidal neovascularization. *Retina* 2008;28(8):1117-1123

18 Silva RM, Ruiz-Moreno JM, Rosa P, Carneiro A, Nascimento J, Rito LF, Cachulo ML, Carvalheira F, Murta JN. Intravitreal Ranibizumab for myopic choroidal neovascularization: 12-month results. *Retina* 2010;30(3):407-412

19 Varano M, Tedeschi M, Oddone F, Perillo L, Coppe AM, Parravano M. Microperimetric retinal changes in myopic choroidal neovascularization treated with intravitreal Ranibizumab. *Retina* 2010;30(3):413-417

20 Heier JS, Brown D, Ciulla T, Abraham P, Bankert JM, Chong S, Daniel PE Jr, Kim IK. Ranibizumab for choroidal neovascularization secondary to causes other than age-related macular degeneration: a phase I clinical trial. *Ophthalmology* 2011;118(1):111-118

21 Lai TY, Chan WM, Liu DT, Lam DS. Intravitreal ranibizumab for the primary treatment of choroidal neovascularization secondary to pathologic myopia. *Retina* 2009;29(6):750-756

22 Lalloum F, Souied EH, Bastuji-Garin S, Puche N, Querques G, Glacet-Bernard A, Coscas G, Soubrane G, Leveziel N. Intravitreal ranibizumab for choroidal neovascularization complicating pathologic myopia. *Retina* 2010;30(3):399-406

23 Wu TT, Kung YH. The 12-month outcome of three consecutive monthly intravitreal injections of Ranibizumabfor myopic choroidal neovascularization. *J Ocul Pharmacol Ther* 2012;28(2):129-133

24 Mones JM, Amselem L, Serrano A, Garcia M, Hijano M. Intravitreal Ranibizumab for choroidal neovascularization secondary to pathologic myopia: 12-month results. *Eye* (*Lond*) 2009;23(6):1275-1280

25 Verteporfin in Photodynamic Therapy (VIP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin,1 year results of a randomized clinical trial-VIP report No. 1. *Ophthalmology* 2001;108(5):841-852

26 Blinder KJ, Blumenkranz MS, Bressler NM, Bressler SB, Donato G, Lewis H, Lim Jl, Menchini U, Miller JM, Mones JM, Potter MJ, Pournaras C, Reaves A, Rosenfeld P, Schachat AP, Schmidt-Erfurth U, Sickenberg M, Singerman LJ, Slakter JS, Strong HA, Virgili G, Williams GA. Verteporfin therapy of subfoveal choroidal neovascularization in pathologic myopia: 2-year results of a randomized clinical trial-VIP report No. 3. *Ophthalmology* 2003;110(4):667-673

27 Wolf S, Balciuniene VJ, Laganovska G, Menchini U, Ohno-Matsui K, Sharma T, Wong TY, Silva R, Pilz S, Gekkieva M, RADIANCE study Group. RADIANCE: a randomized controlled study of Ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. *Ophthalmology* 2014;121(3):682-692

28 Iacono P, Parodi MB, Papayannis A, Kontadakis S, Sheth S, Cascavilla ML, Bandello F. Intravitreal ranibizumab versus bevacizumab for treatment of myopic choroidal neovascularization. *Retina* 2012;32(8):1539-1546

29 Cha DM, Kim TW, Heo JW, Woo SJ, Park KH, Yu HG, Chung H. Comparison of 1-year therapeutic effect of ranibizumab and bevacizumab for myopic choroidal neovascularization: a retrospective, multicenter, comparative study. *BMC Ophthalmol* 2014;14:69