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Comparison of ranibizumab and bevacizumab in neovascular age-related macular degeneration

Huseyin Serdarogullari[1], Muzaffer Ozturk[2], Umur Kayhan[1], Selim Bolukbasi[1], Burak Erden[1], Mustafa Elcioglu[1]

[1]Department of Ophthalmology, Okmeydani Education and Research Hospital, Istanbul 34400, Turkey
[2]Dunya Goz Hastanesi (World Eye Hospital), Istanbul 34400, Turkey
Correspondence to: Huseyin Serdarogullari. Department of Ophthalmology, Okmeydani Training and Research Hospital, Istanbul 34400, Turkey. hus. serdar@ gmail. com
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比较雷珠单抗和贝伐珠单抗对新生血管 AMD 的疗效

Huseyin Serdarogullari[1], Muzaffer Ozturk[2], Umur Kayhan[1], Selim Bolukbasi[1], Burak Erden[1], Mustafa Elcioglu[1]
(作者单位:作者单位:[1]土耳其,伊斯坦布尔,奥克梅达尼教学研究医院眼科;[2]土耳其,伊斯坦布尔,顿尼亚 Goz Hastanesi (世界眼科医院))
通讯作者:Huseyin Serdarogullari. hus. serdar@ gmail. com

摘要

目的:比较玻璃体内注射雷珠单抗与贝伐珠单抗对年龄相关性黄斑变性(age-related macular degeneration, AMD)的疗效,治疗方案必要时采用。

方法:回顾性分析 63 例 63 眼(雷珠单抗治疗组 35 眼,贝伐珠单抗治疗组 28 眼)新确诊新生血管年龄相关性黄斑变性患者的资料。治疗 12mo 后随访,分析比较两组患者的最佳矫正视力(BCVA)和黄斑中心凹厚度(CFT)。采用双尾 t 检验和单因素方差分析比较两组最佳矫正视力和黄斑中心凹厚度的变化。

结果:雷珠单抗治疗组 35 眼和贝伐珠单抗治疗组 28 眼均完成 12mo 随访,并记录数据。雷珠单抗治疗组最佳矫正视力均值增加 0.1logMAR;相反,贝伐珠单抗治疗组最佳矫正视力均值下降 0.06logMAR(P=0.01)。雷珠单抗治疗组 13 眼(37%)和贝伐珠单抗治疗组 4 眼(14%)最佳矫正视力至少增加 0.3logMAR。雷珠单抗治疗组平均黄斑中心凹厚度减少 41.6μm,贝伐珠单抗治疗组减少 8.1μm(P=0.003)。两组平均注射次数是 4.46 次和 4.11 次(P>0.05)。

结论:玻璃体内注射雷珠单抗组在视力和消水肿方面疗效优于贝伐珠单抗组。但是,两种药的疗效和安全性还需要随机的长期临床试验来验证。

关键词:年龄相关性黄斑变性;抗血管内皮生长因子治疗;雷珠单抗;贝伐珠单抗;脉络膜新生血管

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Abstract

• AIM: To compare the efficacy of intravitreal ranibizumab and bevacizumab for the treatment of neovascular age-related macular degeneration (AMD) using a pro re nata (PRN) treatment regimen.

• METHODS: A total of 63 eyes (35 eyes treated with ranibizumab and 28 eyes treated with bevacizumab) of 63 patients with newly diagnosed neovascular AMD were analyzed and compared retrospectively. Outcomes included comparison of best-corrected visual acuity (BCVA) and central foveal thickness (CFT) after ranibizumab or bevacizumab treatment at 12mo follow-up. Two-tailed t-tests and one-way ANOVA were used to compare mean changes in BCVA and CFT for different groups.

• RESULTS: Thirty-five eyes treated with ranibizumab and 28 eyes treated with bevacizumab were enrolled and completed 12mo follow-up. At 12mo, mean BCVA increased by 0.1logMAR with ranibizumab treatment; however BCVA decreased by 0.06logMAR with bevacizumab treatment (P=0.01). A gain of at least 0.3logMAR in BCVA was observed in 13 eyes (37%) treated with ranibizumab and in 4 eyes (14%) treated with bevacizumab. Mean CFT reduced by 41.6μm and 8.1μm in the ranibizumab and bevacizumab groups, respectively (P=0.003). The mean number of injections per eye was 4.46 with ranibizumab and 4.11 with bevacizumab (P>0.05).

• CONCLUSION: Intravitreal ranibizumab yielded better visual and anatomical results than bevacizumab. However, randomized long-term clinical trials are needed to draw conclusions about efficacy and safety of the two drugs.

• KEYWORDS: age-related macular degeneration; anti-VEGF therapy; ranibizumab; bevacizumab; choroidal neovascularization
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INTRODUCTION

Age-related macular degeneration (AMD) is the most common cause of severe central vision loss in the population over the age of 50 years in many developed countries. Choroidal neovascularization (CNV) secondary to

AMD, which is also known as 'wet' or 'exudative' type AMD, causes severe visual impairment and influence the quality of life[1-7]. Recent innovations in technology have shown that the neovascular process is generated by vascular endothelial growth factor (VEGF-A)[8]. In the light of these advances, intravitreal injection of VEGF inhibitors has become the most important therapeutic option for neovascular AMD.

Intravitreal anti-VEGF treatment with ranibizumab (Lucentis®, Novartis Pharma AG, Basel, Switzerland and Genentech, South San Francisco, California, USA) and bevacizumab (Avastin®, Genentech, South San Francisco, California, USA) has changed the approach of ophthalmologists in the management of this disease, as both of these have shown encouraging results with stabilization or even improvement of visual acuity[9-13]. The Food and Drug Administration (FDA) originally approved bevacizumab, which is a larger full-length, recombinant, humanized, monoclonal antibody, for intravenous treatment of metastatic colorectal cancer in 2004. On the other hand, ranibizumab is a recombinant, humanized, monoclonal Fab fragment and was approved by the FDA for the intravitreal treatment of neovascular AMD in 2006[13,14]. Some studies compared full-length bevacizumab with the Fab version of bevacizumab in primate and rabbit eyes. These studies showed that Fab achieved to diffuse subretinal space but IgG was not capable of passing through inner retinal layers[15,16]. Hence, ranibizumab was thought as a more effective treatment for CNV. There are many multicenter controlled clinical trials that reported remarkable results with ranibizumab in treatment of neovascular AMD[8,12,17,18].

The preference of anti-VEGF treatment mostly depended on the cost-effectiveness and availability of the drug. Ranibizumab seems to be considerably more expensive than bevacizumab, despite similar benefits are provided by both drugs. Although the safety and efficacy of bevacizumab has not been well established, bevacizumab has been the drug of choice because of its cost. There are several multicenter, randomized ongoing clinical trials to compare the efficacy of both drugs for treating neovascular AMD (VIBERA NCT00559715, IVAN CTEU Bristol, MANTA NCT00710229, LUCAS NCT01127360 AND GEFAL NCT01170767 trials). Recently, the Comparison of Age-related Macular Degeneration Treatment Trials (CATT), which compared bevacizumab and ranibizumab in fixed monthly or as-needed regimen of treatment, have indicated similar efficacy of the two drugs. On the other hand, pro re anta (PRN) dosing of bevacizumab was found inferior compared to monthly dosing of ranibizumab or bevacizumab[13]. The purpose of our study was to compare the efficacy of intravitreal ranibizumab and bevacizumab at one year for the treatment of neovascular AMD using PRN regimen.

SUBJECTS AND METHODS

Inthis retrospective, non-randomized and unicentric study (Okmeydani Training and Research Hospital, Istanbul, Turkey), medical records of 63 patients with neovascular AMD were reviewed. The study followed the tenets of the Declaration of Helsinki and all patients signed an informed consent. Patients were included in our study if they had subfoveal CNV secondary to AMD diagnosed both clinically and on fundus fluorescein angiography. Exclusion criteria consisted of having a previous treatment for neovascular AMD such as argon laser, photodynamic, or intravitreal anti-VEGF therapy or having an accompanying ocular disease. Only the right eye was included in patients who were diagnosed with neovascular AMD in both eyes.

In the study, we included a total of 63 patients, 35 patients treated with ranibizumab and 28 patients treated with bevacizumab. Prior to treatment, all patients had undergone a complete ophthalmic examination that included best corrected visual acuity (BCVA) measurement with Snelling chart, slit-lamp biomicroscopy, fundus examination, fundus fluorescein angiography (FFA) and spectral domain optical coherence tomography (SD-OCT) with Cirrus™ HD-OCT (Carl Zeiss Meditec, Dublin, CA, USA). OCT images included macular cube and high definition raster scans that were obtained by the same examiner. Foveal thickness was automatically calculated by OCT mapping software and the images were interpreted by an experienced examiner. CNV lesions were categorized angiographically into predominantly classic, minimally classic or occult with no classic.

Patients were treated with initial 3 monthly intravitreal injections of 0.5mg of ranibizumab or 1.25mg of bevacizumab. Intravitreal injections were performed in an operating room under sterile conditions. The eye was anesthetized with proparacaine HCl 0.5% drops and povidone iodine 5% was applied over the injection site with a cotton-tipped applicator. The drug was injected with a 30-gauge needle into the vitreous cavity through the pars plana, 3.5mm in pseudophakic and 4mm in phakic eyes posterior to the limbus. Topical moxifloxacin was used for five days after the procedure. All patients were re-evaluated typically one month after each treatment. After the third injection, re-injection was recommended for each patient on individual basis. The indication for re-treatment was based on presence of new macular hemorrhage, subretinal or intraretinal fluid on OCT or leakage on FFA.

Statistical Analysis Outcomes obtained from the study included a baseline BCVA and CFT, BCVA and CFT at the end of follow-up (12 months after first injection), and total number of injections administered over 1 year. Statistical analysis was carried out using SPSS 20 (SPSS Inc., Chicago, IL, USA). Two-tailed t-tests and one-way ANOVA were used to compare mean changes in BCVA and CFT for different groups. For statistical analysis, Snelling BCVA scores were converted into the logarithm of minimum angle of resolution (logMAR). For comparison with number of letters (Early Treatment Diabetic Retinopathy Study [ETDRS]), a 0.3logMAR is equivalent to 3 lines or 15 letters. A P value of <0.05 was considered statistically significant.

RESULTS

Thirty-five eyes of 35 patients in the ranibizumab group and twenty-eight eyes of 28 patients in the bevacizumab group with a total of sixty-three eyes of 63 patients were included in the study. The distribution of age and gender was similar in both groups. In the ranibizumab group, mean age was (66.4±7.2) years. There were 20 (57.1%) male and 15 (42.9%) female. Fifteen (42.8%) patients were phakic and 20 (57.2%) were pseudophakic. Of the patients treated with ranibizumab, 28.6% had predominantly classic, 25.7% had minimally classic and 45.7% had occult CNV. In the bevacizumab group, mean age was (68.3±7.1) years. There were 13 (46.4%) male and 15 (53.6%) female. Eleven (39.3%) patients were phakic and 17 (60.7%) were pseudophakic. Of the patients treated with bevacizumab, 42.9% had predominantly classic, 25.0% had minimally classic and 32.1% had occult CNV. The characteristics at baseline of both groups are summarized in Table 1.

Table 1 Baseline characteristics of the patients $\bar{x}\pm s$

Variable	Ranibizumabgroup (n=35)	Bevacizumabgroup (n=28)
Age (a)	66.4±7.2	68.3±7.1
Gender (%)		
Male	57.1	46.4
Female	42.9	53.6
Laterality (%)		
Right	37.1	53.6
Left	62.9	46.4
Lens status (%)		
Phakic	42.8	39.3
Pseudophakic	57.2	60.7
Subtype of CNV lesion (%)		
Predominantly classic	28.6	42.9
Minimally classic	25.7	25.0
Occult	45.7	32.1
Baseline BCVA (logMAR)	1.24±0.52	0.92±0.45
Baseline CFT (μm)	358.9±83.4	337.1±55.5

CNV: Choroidal neovascularization; BCVA: Best-corrected visual acuity; CFT: Central foveal thickness.

In the ranibizumab group (n=35), mean logMAR equivalent BCVA improved from 1.24±0.52logMAR to 1.14±0.46logMAR with a mean gain of 0.1±0.25logMAR (5 letters) (P=0.02). In the bevacizumab group (n=28), mean logMAR equivalent BCVA decreased from 0.92±0.45logMAR to 0.98±0.51logMAR, with a mean loss of 0.06±0.25logMAR (3 letters) (P>0.05). There was statistically significant difference between the two groups in the change of BCVA at the end of 12mo (P=0.01). Visual gain occurred in 48.6% (n=17) of eyes treated with ranibizumab and 21.4% (n=6) of eyes treated with bevacizumab. BCVA remained unchanged in 31.4% (n=11) in eyes treated with ranibizumab and 35.7% (n=10) of eyes treated with bevacizumab. BCVA decreased in 20.0% (n=7) of eyes treated with ranibizumab and 42.9% (n=12) of eyes treated with bevacizumab. At 12mo, 89% of the patients who were treated with ranibizumab lost less than 0.3logMAR (<15 letters on the ETDRS chart), as compared with 86% in the bevacizumab group. At 1 year of follow-up, a gain of at least 0.3logMAR (≥15 letters on ETDRS chart) was observed in 37% of the patients in the ranibizumab group and 14% of the patients in the bevacizumab group. In addition, there were no statistically significant differences between CNV lesion subgroups in terms of change in logMAR BCVA in the ranibizumab and bevacizumab groups (P>0.05). Mean logMAR BCVA for each subtype (predominantly classic, minimally classic and occult lesions) of both groups are presented in Table 2.

Mean baselineCFT was statistically similar between the groups (358.9±83.4μm in the ranibizumab group and 337.1±55.5μm in the bevacizumab group; P>0.05). Mean final CFT was 317.3±73.7μm in the ranibizumab group and 329.0±57.2μm in the bevacizumab group (P>0.05). The difference in the mean reduction of CFT between the groups was statistically significant at 12mo of follow-up (ranibizumab: −41.6±47.5μm *vs* bevacizumab: −8.1±39.4μm, P=0.003). There were no statistically significant differences between CNV lesion subgroups in terms of change in CMT in the ranibizumab and bevacizumab groups (P>0.05). Mean CFT for each subtype (predominantly classic, minimally classic and occult lesions) of both groups are presented in Table 2.

The mean number of injections performed in each eye was (4.46±1.04) for the ranibizumab group and (4.11±1.45) for the bevacizumab group over 12 months. There was no statistically significant difference between two groups (P>0.05). Following the first 3 injections, a dry macula was achieved in 6 (17.1%) and 5 (17.8%) of eyes in the ranibizumab and bevacizumab groups, respectively. The number of injections to obtain a dry macula in both groups is shown in Table 3.

None of the patients in both groups had major ocular complications such as intraocular inflammation, endophthalmitis, retinal detachment, cataract, glaucoma or systemic complications. Intraocular pressure (IOP) values were within the normal range (10-21mmHg) during the follow-up period. Mild subconjunctival hemorrhage over the site of injection was observed in 18% of all eyes.

DISCUSSION

In this non-randomized, single-center, retrospective analysis, ranibizumab was found to achieve slightly better results than bevacizumab for the management of neovascular AMD. In the ranibizumab group, themean gain in BCVA was around 5 letters with a number of nearly 4 injections at 12 months. On the other hand, there was a mean loss of approximately 3 letters with a mean number of nearly 4 injections at 12mo in the bevacizumab group though this decrease was not statistically significant.

In our study, visual outcomes of eyes treated with ranibizumab are compatible with the results of randomized, multicenter clinical trials such as MARINA, ANCHOR and PIER. A comparable proportion of patients who had lost less than 0.3logMAR at the end of the follow-up was seen(89%, as

Table 2 Mean BCVA of each CNV lesion subgroup

Variable	Ranibizumab			Bevacizumab		
	PC	MC	Occ	PC	MC	Occ
BCVA at baseline(logMAR)	1.44±0.62	1.10±0.51	1.20±0.46	0.98±0.49	0.93±0.46	0.82±0.43
BCVA at 12mo (logMAR)	1.28±0.52	1.15±0.44	1.05±0.44	1.12±0.62	0.89±0.53	0.85±0.29
CFT at baseline (μm)	351.2±72.4	385.6±81.3	348.7±92.2	351.1±60.2	341.6±64.1	314.8±37.3
CFT at 12mo (μm)	304.5±44.7	343.4±90.1	310.6±78.8	351.8±68.9	324.3±53.0	302.1±28.1

BCVA: Best-corrected visual acuity; CFT: Central foveal thickness; PC: predominantly classic; MC: minimally classic; Occ: occult.

Table 3 Number of injections to obtain a dry macula *n*(%)

Number of injections	Ranibizumab	Bevacizumab
3	6 (17.1)	5 (17.8)
4	15 (42.9)	8 (28.6)
5	6 (17.1)	6 (21.4)
6	8 (22.9)	7 (25.0)
7	0 (0)	1 (3.6)
8	0 (0)	1 (3.6)
Mean±SD	4.46±1.04	4.11±1.45

compared to 94.6% in the MARINA study; 96.4% in the ANCHOR study; 90.2% in the PIER study)[8,12,22]. Our results are also similar with those of the PrONTO study, in which 95% of eyes lost less than three lines of vision, 35% gained three or more lines, with a mean of 5.6 injections[23,24]. Additionally, a dry macula was obtained after the first 3 monthly injections in 17% of our patients in both groups during the 12mo follow-up.

Withthe increase in the number of patients seeking treatment for neovascular AMD, there has been great debate about the efficacy and safety of ranibizumab and bevacizumab. So far, there had been some large, double-blinded, multicentric randomized clinical trials presenting ranibizumab as the only drug to improve mean BCVA in patients with neovascular AMD[8,17,28]. Although bevacizumab, which is considerably cheaper than ranibizumab, demonstrated encouraging results in the CATT trial[8], ABC trial[19] and some published case series, many ophthalmologists are concerned about its efficacy and safety[9,11,20]. There are some larger, randomized ongoing clinical trials comparing the two anti-VEGF drugs.

In most published papers, ranibizumab and bevacizumab were investigated separately regarding the efficacy and safety of the two molecules. The only head-to-head comparison between the two drugs was carried out in the CATT, which was a multicenter, non-inferiority study comparing ranibizumab and bevacizumab in monthly or PRN regimens of treatment. The results indicated that both molecules can achieve visual improvement; yet, bevacizumab was shown to be more profitable than ranibizumab. The main outcome of the CATT was that monthly dosing of bevacizumab compared to ranibizumab was non-inferior; however the PRN regimen of bevacizumab was not found non-inferior[13]. Although no difference in VA scores between ranibizumab and bevacizumab groups was found in the CATT study, our study showed BCVA improvement of 0.10logMAR in the ranibizumab group, but worsening in BCVA by 0.06logMAR in the bevacizumab group after 12mo. The proportion of patients who had lost less than 0.3logMAR at the end of the 12mo was similar in the two groups comparing to those of CATT study (89% and 86% *vs* 95.4% and 91.5%). Moreover, a higher proportion of patients had a gain of at least 0.3logMAR in the ranibizumab group comparing to bevacizumab group (37% *vs* 14%). In contrast to CATT[13] and other studies[24-28], there was a significant difference in the mean change of CFT between the two groups with the same regimen of treatment.

Comparison of outcomes after switching treatment from bevacizumab to ranibizumab in neovascular AMD was reported by Kent *et al*[29]. The study showed that there had been a significant improvement in BCVA and CFT in patients with neovascular AMD initially treated with bevacizumab. After switching to ranibizumab, there had been a further significant improvement in BCVA and a decline in retinal thickness. It was shown that ranibizumab can maintain, or improve the effect achieved after an initial course of bevacizumab[29].

In our study, ranibizumab yielded better results at 12mo. Some authors believe that ranibizumab is more effective than bevacizumab due to ranibizumab being asmaller molecule and having capacity to penetrate retina more easily than bevacizumab. In a retrospective study, Chang *et al*[30] found that ranibizumab treated eyes were more likely to have improvement in OCT parameters in the short-term. On the other hand, bevacizumab is believed to have longer-term effects than ranibizumab, due to slower clearance from the eye because of its larger size[31]. Some researchers concluded that patients who developed tachyphylaxis to one treatment may respond well to another treatment. Gasperini *et al*[32] found that 81% cases had shown some response after switching therapies[32]. In a retrospective study, Aslankurt *et al*[33] demonstrated that switching bevacizumab to ranibizumab had been superior to switching ranibizumab to bevacizumab[33].

There are some limitations to our study. The data were collected retrospectively from a single-center with a relatively small sample size, that is not sufficient to have a strong opinion about efficacy and safety.

In conclusion, there are many factors which may influence the efficacy and safety of the two drugs. Although, the choice of drug should target improving the quality of life of patients with AMD in the first place, economical issues may also be considered. An approach based on the needs and clinical picture of a patient appears to be appropriate for the treatment of neovascular AMD.

REFERENCES

1 Bressler NM, Bressler SB, Congdon NG, Ferris FL 3rd, Friedman DS, Klein R, Lindblad AS, Milton RC, Seddon JM; Age-Related Eye Disease Study Research Group. Potential public health impact of Age-Related Eye Disease Study results: AREDS report no 11. *Arch Ophthalmol* 2003;121(11):1621-1624

2 Klein R, Peto T, Bird A, Vannewkirk MR. The epidemiology of age-related macular degeneration. *Am J Ophthalmol* 2004;137(3):486-495

3 Congdon N, O'Colmain B, Klaver CC, Klein R, Muñoz B, Friedman DS, Kempen J, Taylor HR, Mitchell P; Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol* 2004;122(4):477-485

4 Friedman DS, O'Colmain BJ, Muñoz B, Tomany SC, McCarty C, de Jong PT, Nemesure B, Mitchell P, Kempen J; Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol* 2004;122(4):564-572

5 Vingerling JR, Dielemans I, Hofman A, Grobbee DE, Hijmering M, Kramer CF, de Jong PT. The prevalence of age-related maculopathy in the Rotterdam Study. *Ophthalmology* 1995;102(2):205-210

6 Kahn HA, Leibowitz HM, Ganley JP, Kini MM, Colton T, Nickerson RS, Dawber TR. The Framingham Eye Study. I. Outline and major prevalence findings. *Am J Epidemiol* 1977;106(1):17-32

7 Foran S, Wang JJ, Mitchell P. Causes of visual impairment in two older population cross-sections: the Blue Mountains Eye Study. *Ophthalmic Epidemiol* 2003;10(4):215-225

8 Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355(14):1419-1431

9 Spaide RF, Laud K, Fine HF, Klancnik JM Jr, Meyerle CB, Yannuzzi LA, Sorenson J, Slakter J, Fisher YL, Cooney MJ. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006;26(4):383-390

10 Rosenfeld PJ, Moshfeghi AA, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration. *Ophthalmic Surg Lasers Imaging* 2005;36(4):331-335

11 Bashshur ZF, Haddad ZA, Schakal A, Jaafar RF, Saab M, Noureddin BN. Intravitreal bevacizumab for treatment of neovascular age-related macular degeneration: a one-year prospective study. *Am J Ophthalmol* 2008;145(2):249-256

12 Brown DM, Michels M, Kasier PK, Heier JS, Sy JP, Ianchulev T; ANCHOR Study Group. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. *Ophthalmology* 2009;116(1):57-65

13 Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011;364(20):1897-1908

14 Steinbrook R. The price of sight-ranibizumab, bevacizumab, and the treatment of macular degeneration. *N Engl J Med* 2006;355:1409-1412

15 Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. *Retina* 2006;26(8):859-870

16 Mordenti J, Cuthbertson RA, Ferrara N, Thomsen K, Berleau L, Licko V, Allen PC, Valverde CR, Meng YG, Fei DT, Fourre KM, Ryan AM. Comparisons of the intraocular tissue distribution, pharmacokinetics, and safety of 125I-labeled full-length and Fab antibodies in rhesus monkeys following intravitreal administration. *Toxicol Pathol* 1999;27(5):536-544

17 Kaiser PK, Blodi BA, Shapiro H, Acharya NR. Angiographic and optical coherence tomographic results of the MARINA study of ranibizumab in neovascular age-related macular degeneration. *Ophthalmology* 2007;114(10):1868-1875

18 Mitchell P, Korobelnik JF, Lanzetta P, Holz FG, Prünte C, Schmidt-Erfurth U, Tano Y, Wolf S. Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. *Br J Ophthalmol* 2010;94(1):2-13

19 Tufail A, Patel PJ, Egan C, Hykin P, da Cruz L, Gregor Z, Dowler J, Majid MA, Bailey C, Mohamed Q, Johnston R, Bunce C, Xing W; ABC Trial Investigators. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. *BMJ* 2010;340:c2459

20 Goff MJ, Johnson RN, McDonald HR, Ai E, Jumper JM, Fu A. Intravitreal bevacizumab for previously treated choroidal neovascularization from age-related macular degeneration. *Retina* 2007;27(4):432-438

21 Regillo CD, Brown DM, Abraham P, Yue H, Ianchulev T, Schneider S, Shams N. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol* 2008;145(2):239-248

22 Lalwani GA, Rosenfeld PJ, Fung AE, Dubovy SR, Michels S, Feuer W, Davis JL, Flynn HW Jr, Esquiabro M. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. *Am J Ophthalmol* 2009;148(1):43-58. e1

23 Fung AE, Lalwani GA, Rosenfeld PJ, Dubovy SR, Michels S, Feuer WJ, Puliafito CA, Davis JL, Flynn HW Jr, Esquiabro M. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol* 2007;143(4):566-583

24 Stepien KE, Rosenfeld PJ, Puliafito CA, Feuer W, Shi W, Al-Attar L, Dubovy SR, Murray TG, Davis JL, Lee WH, Schwartz SG, Smiddy WE, Berrocal AM, Flynn HW Jr. Comparison of intravitreal bevacizumab followed by ranibizumab for the treatment of neovascular age-related macular degeneration. *Retina* 2009;29(8):1067-1073

25 Landa G, Amde W, Doshi V, Ali A, McGevna L, Gentile RC, Muldoon TO, Walsh JB, Rosen RB. Comparative study of intravitreal bevacizumab (avastin) versus ranibizumab (lucentis) in the treatment of neovascular age-related macular degeneration. *Ophthalmologica* 2009;223(6):370-375

26 Gamulescu MA, Radeck V, Lustinger B, Fink B, Helbig H. Bevacizumab versus ranibizumab in the treatment of exudative age-related macular degeneration. *Int Ophthalmol* 2010;30(3):261-266

27 Carneiro AM, Mendonça LS, Falcão MS, Fonseca SL, Brandão EM, Falcão-Reis FM. Comparative study of 1+PRN ranibizumab versus bevacizumab in the clinical setting. *Clin Ophthalmol* 2012;6:1149-1157

28 Bellerive C, Cinq-Mars B, Lalonde G, Malenfant M, Tourville E, Tardif Y, Giasson M, Hébert M. Bevacizumab and ranibizumab for neovascular age related macular degeneration: a treatment approach based on individual patient needs. *Can J Ophthalmol* 2012;47(2):165-169

29 Kent JS, Iordanous Y, Mao A, Powell AM, Kent SS, Sheidow TG. Comparison of outcomes after switching treatment from intravitreal bevacizumab to ranibizumab in neovascular age-related macular degeneration. *Can J Ophthalmol* 2012;47(2):159-164

30 Chang TS, Kokame G, Casey R, Prenner J, Feiner L, Anderson N. Short-term effectiveness of intravitreal bevacizumab versus ranibizumab injections for patients with neovascular age-related macular degeneration. *Retina* 2009;29(9):1235-1241

31 Klettner AK, Kruse ML, Meyer T, Wesch D, Kabelitz D, Roider J. Different properties of VEGF-antagonists: bevacizumab but not ranibizumab accumulates in RPE cells. *Graefes Arch Clin Exp Ophthalmol* 2009;247(12):1601-1608

32 Gasperini JL, Fawzi AA, Khondkaryan A, Lam L, Chong LP, Eliott D, Walsh AC, Hwang J, Sadda SR. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation. *Br J Ophthalmol* 2012;96(1):14-20

33 Aslankurt M, Aslan L, Aksoy A, Erden B, Cekiç O. The results of switching between 2 anti-VEGF drugs, bevacizumab and ranibizumab, in the treatment of neovascular age-related macular degeneration. *Eur J Ophthalmol* 2013;23(4):553-557