• Original Article •

Long-term outcomes of ranibizumab treatment in neovascular age-related macular degeneration

Burak Simsek, Aylin Ardagil Akcakaya, Isilay Ozsoy Koyun, Sevil Ari Yaylali

Istanbul Medeniyet University, Goztepe Research Hospital, Department of Ophthalmology, Istanbul 34722, Turkey

Correspondence to: Burak Simsek. Istanbul Medeniyet University, Goztepe Research Hospital, Istanbul 34704, Turkey. drburaksimsek@gmail.com

Received: 2018-11-20 Accepted: 2019-12-23

Abstract

● AIM: To investigate 3-year results in our neovascular age related macular degeneration (NV-AMD) patients treated with ranibizumab.

● METHODS: Retrospective study. Visual acuity (VA), a full biomicroscopic examination (anterior segment and fundus), and optical coherence tomography (OCT) findings were noted at every visit. All patients were followed monthly. The VA values for the visits closest to 12, 24, and 36mo were analysed. 101 eyes of 73 patients were enrolled. According to the initial VA, the patients were divided three groups: initial VA ≤35 (Group 1), 36-54 (Group 2), and ≥55 letters (Group 3). After three loading doses of 0.5 mg ranibizumab if retreatment was needed, again, 0.5 mg ranibizumab was administered

● RESULTS: Totally 57 of the 101 eyes were from males and 44 were from females. The average age was 75.1 years. The difference on the changes of VA among three groups at 24 and 36mo were statistically significant (*P*=0.02 and 0.001 respectively). At the end of the 36-month follow-up the VA increase in Group 2 was significant (*P*=0.001). At the 12, 24, and 36mo visits most of the eyes showed no VA loss and most of these eyes were in Group 1. The average number of injections administered was 7.3 and the average number of visits was 23.9 during the follow-up.

● CONCLUSION: VA improvement was significant in those with mild initial VA (36-54 letters). Most eyes showed no VA loss regardless of the initial VA. No correlation between the final VA and the average number of injections.

● KEYWORDS: Neovascular; age related macular degeneration; long term; ranibizumab

DOI:10.18240/ier.2020.02.07

Citation: Simsek B, Ardagil Akcakaya A, Ozsoy Koyun I, Ari Yaylali S. Long-term outcomes of Ranibizumab treatment in neovascular age-related macular degeneration. *Int Eye Res* 2020;1(2):102-107

INTRODUCTION

Neovascular age-related macular degeneration (NV-AMD) is a chronic, progressive disorder. In developed countries, it is one of the leading causes of irreversible central vision loss[1]. By 2030, in industrialised countries, it is expected that NV-AMD will be the major reason for blindness, passing diabetic retinopathy and glaucoma[2]. An increase in its prevalence is anticipated with the aging population[3].

In tzhe treatment of NV-AMD, inhibition of ocular vascular endothelial growth factor (VEGF) is currently the standard modality (anti-VEGF). Anti-VEGF prevents the final outcomes, such as choroidal neovascularisation and vascular leakage[4]. In anti-VEGF treatment, the currently available agents are ranibizumab and aflibercept. Before the availability of these agents, bevacizumab had been used in an off-label manner[5]. Since the approval of ranibizumab by the Food and Drug Administration (FDA) in 2006, it has been used widely for ocular anti-VEGF treatment.

Although many clinical studies have been reported regarding the efficacy of ranibizumab, there are few reflecting its long-term clinical use. One of the most recent studies about long term outcomes of ranibizumab with treat and extend regimen in NV-AMD reports 8-year results[6]. In this study it was shown that during 4y mean VA is significantly better than first visit with ranibizumab. Yet after 4y mean VA started to decline and after 8y it was even under the first visit value because of the macular atrophy. In another recent study about long term outcomes of ranibizumab therapy in NV-AMD with pro-re-nata (PRN) regimen, it was showed that after 5y half of the patients preserved their VA regarding initial VA[7]. VEGF Trap-Eye Investigation of Efficacy and Safety in Wet AMD (VIEW) studies are another large and long term studies about antiVEGF therapy in NV-AMD. VIEW studies were designed to particularly investigate the most recent antiVEGF agent aflibercept. In VIEW studies, the efficacy of aflibercept was compared to ranibizumab. One of the major outcomes of this study was preservation of VA in long term (96wk) not only in ranibizumab group but also in aflibercept groups[8-10]. In this

study, we investigated 3-year results in our NV-AMD patients treated with ranibizumab.

SUBJECTS AND METHODS

Ethical Approval This study was carried out in accordance with Helsinki Declaration and approved by the ethic committee. Informed consent was waived due to the retrospective nature of the study.

The files of NV-AMD patients followed in our clinic for at least 3y with a ranibizumab PRN regimen after three loading doses were investigated retrospectively. The inclusion criteria were age 50 and older, a diagnosis of primary or recurrent choroidal neovascular membrane (CNVM) secondary to NV-AMD, and at least a 36-month follow-up period. Patients with CNVM secondary to a non-AMD aetiology, patients with systemic contraindications for anti-VEGF therapy, and patients with a history of intravitreal bevacizumab or triamcinolone treatment or photodynamic therapy (PDT) were excluded. Regarding inclusion, no threshold value was considered for visual acuity (VA). The genders and ages of the patients were recorded. Initially, fundus fluorescein angiography (FFA) imaging was performed in all patients. VA, a full biomicroscopic examination (anterior segment and fundus), and optical coherence tomography (OCT) findings were noted at every visit. VA was measured at 4m with the early treatment diabetic retinopathy study (ETDRS) chart. OCT and FFA imaging, as needed, were performed with a Topcon 3D OCT 2000 (TOPCON, Japan) device. All patients were followed monthly. The VA values for the visits closest to 12, 24, and 36mo were analysed. The interval between the retreatment indication date and the injection date was set for a maximum of 2wk.

In total, 101 eyes of 73 patients were enrolled. According to the initial VA, the patients were divided three groups: initial VA ≤35 (Group 1), 36-54 (Group 2), and ≥55 letters (Group 3). After three loading doses of 0.5 mg ranibizumab, in determining retreatment in follow-up visits, recent or persistent intraretinal or subretinal fluid in OCT, CNVM progression findings, such as recent haemorrhage beside the lesion in biomicroscopy, VA loss of at least five letters, and leakage or hyperfluorescence in FFA were accepted as indicators of activation. If retreatment was needed, again, 0.5 mg ranibizumab was administered. Statistically, Dunn's multiple comparison test was applied to the data and *P* value less than 0.05 was considered significantly in the study.

RESULTS

In total, 101 eyes of 73 patients were enrolled. The disease was bilateral in 28 of the 73 patients.

Demographic Characteristics In total, 57 of the 101 eyes were from males and 44 were from females. The average age was 75.1 years.

Visual Acuity There were 65 (64.4%) eyes in Group 1, 30 (29.7%) in Group 2, and 6 (5.9%) in Group 3. The average VA changes in 12mo were -3.57, +3.4, and +2.0 letters, respectively. The VA changes were not statistically significantly different versus the initial VA (*P*=0.057). The VA changes in the groups at 24mo were -1.68, +10.2, and +10.5 letters, respectively, and all were statistically significantly different in comparison with the initial VA (*P*=0.02). At the 36-month visit, the VA changes were +0.72, +21.47, and +14.83 letters, respectively, and the differences in comparison with the initial VA were significant (*P*=0.0001).

At the end of the 36-month follow-up, the VA in Groups 1 and 3 had increased. However, these increases were not statistically significant. However, the VA increase in Group 2 was significant (*P*=0.001; Table 1).

At the 12-month visit, 75.2% of the eyes showed no VA loss. Thus, the VA was either stable (±5 letters *vs* the initial VA) or gained >5 letters. At 12th month, 57.4% eyes were stable. Most of the stable ones (65%) were in Group 1. In 9.9% of the eyes, the gain was >15 letters and most of them (60%) were in Group 2. In 9.9% of the eyes, the loss was >15 letters and these were all in Group 1.

At the 24-month visit, 78.2% of the eyes showed no VA loss. At 24th month, 51.4% eyes had stable VA and most of them (71.1%) were in Group 1. In 19.8% of the eyes, the gain was >15 letters; most (50%) were in Group 2. In 10.8% of the eyes, the loss was > 15 letters and these were all in Group 1.

At the 36-month visit, 81.1% of the eyes showed no VA loss. At 36th month, 45.5% eyes had stable VA and most of them (78.2%) were in Group 1. In 24.7% of the eyes, the gain was >15 letters; most (48%) were again in Group 2. In 9.9% of the eyes, the loss was >15 letters and these were all in Group 1 (Table 2).

Numbers of Visits and Injections During the follow-up period, the average number of injections administered was 7.3 (Table 3). The average numbers were 7.0, 8.2, and 5.8 in Groups 1, 2, and 3, respectively. Only the differences between groups on the follow up duration was statistically significant.

The average number of visits was 23.9 during the follow-up period. There was no statistically significant difference between the groups (Table 4).

DISCUSSION

When NV-AMD is not treated, it is expected that the VA will decline by three rows in 1y and four rows in 2y[11]. Many studies about the treatment of NV-AMD have been reported over the years. In Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) studies, it was shown that VA loss in NV-AMD could be prevented by monthly ranibizumab Neovascular Age-Related Macular Degeneration Treated with intraocular Ranibizumab (PrONTO) and Comparison of Age-

Table 1 VA changes at 12, 24, and 36mo

Groups	Initial VA (logMAR)	*n*	VA change in 12th month	VA change in 24th month	VA change in 36th month	*P*
Group 1	≤35 letters (0.99±0.4)	65 (64.4%)	-3.57±11.6 -1 (-10.5 to 2)	-1.68±14.49 0 (-7 to 4)	0.72±14.48 0 (-5.5 to 5)	0.292
Group 2	36-54 letters (0.22±0.09)	30 (29.7%)	3.4±10.36 0 (-4.25 to 10)	10.2±16.85[a,b] 5 (-5 to 21.25)	21.47±17[d,e] 23 (5.75-37.25)	0.001
Group 3	≥ 55 letters (0.05±0.08)	6 (5.9%)	2±5.1 1 (-1.25 to 6.25)	10.5±7.31[c] 7.5 (5-17)	14.83±14.09[f] 11 (4.5-23.75)	0.058
P	-	-	0.057	0.002	0.0001	-

[a]Compared to the VA change of Group 1 in 24th month, *P*=0.009; [b]Compared to the VA change of Group 3 in 24th month, *P*=0.537; [c]Compared to the VA change of Group 1 in 24th month, *P*=0.004; [d]Compared to the VA change of Group 1 in 36th month, *P*=0.0001; [e]Compared to the VA change of Group 3 in 36th month, *P*=0.457; [f]Compared to the VA change of Group 1 in 36th month, *P*=0.01.

Table 2 Analysis of VA changes at 12, 24, and 36mo

Follow up time	VA chage	Group 1		Group 2		Group 3		Total	
12th month	±5 letters gain/loss	38	58.46%	15	50.00%	5	83.33%	58	57.43%
	6-15 letters gain	3	4.62%	4	13.33%	1	16.67%	8	7.92%
	≥15 letters gain	4	6.15%	6	20.00%	0	0	10	9.90%
	6-15 letters loss	10	15.38%	5	16.67%	0	0	15	14.85%
	≥15 letters loss	10	15.38%	0	0	0	0	10	9.90%
24th month	±5 letters gain/loss	37	56.92%	12	40.00%	3	50.00%	52	51.49%
	6-15 letters gain	2	3.08%	4	13.33%	1	16.67%	7	6.93%
	≥ 15 letters gain	8	12.31%	10	33.33%	2	33.33%	20	19.80%
	6-15 letters loss	7	10.77%	4	13.33%	0	0.00%	11	10.89%
	≥15 letters loss	11	16.92%	0	0	0	0.00%	11	10.89%
36th month	±5 letters gain/loss	36	55.38%	7	23.33%	3	50.00%	46	45.54%
	6-15 letters gain	3	4.62%	7	23.33%	1	16.67%	11	10.89%
	≥15 letters gain	11	16.92%	12	40.00%	2	33.33%	25	24.75%
	6-15 letters loss	5	7.69%	4	13.33%	0	0	9	8.91%
	≥15 letters loss	10	15.38%	0	0	0	0	10	9.90%

Table 3 Follow-up duration and number of visits and injections

Parameters	Group 1 (*n*=65)	Group 2 (*n*=30)	Group 3 (*n*=6)	*P*
Follow up (mo)	52.77±14.66 49 (42-61.5)	53.07±17.6 45.5 (39.75-66.75)	73.67±23.52 67 (54-99.5)	0.041
No. of visits	23.35±6.6 24 (18-28)	24.07±12.28 20 (17-27.25)	29.5±10.84 30.5 (19-39)	0.327
No. of injections	7.08±4.03 7 (3.5-9)	8.23±5.98 7 (4-11)	5.83±5.74 4 (2.5-8.75)	0.313

Table 4 The correlation of VA change with the follow-up duration, the number of visits and the number of injections

VA Change		Follow-up	No. of visits	No. of injections
12th month	r	-0.096	-0.046	0.066
	P	0.34	0.649	0.512
24th month	r	-0.274	-0.12	0.087
	P	0.006	0.232	0.385
36th month	r	-0.185	-0.119	0.153
	P	0.064	0.234	0.127

Related Macular Degeneration Treatments Trials (CATT) studies for the treatment of NV-AMD, the results of monthly ranibizumab injection and PRN regimens were similar[13-14]. In the regimen, “treat and prolong” monthly injections are performed initially and then the follow-up interval is extended unless neovascularisation signs are seen. Gupta *et al*[15] reported good results with fewer visits by applying such a “treat and extend” regimen. In our clinic, we follow the patients with a PRN regimen after three initial loading doses.

The visual prognosis of NV-AMD is related to age, anatomical characteristics, and initial VA[2,16]. However, the influence of initial VA on final VA has been controversial. For example, when patients who gained or lost at least 15 letters in the ANCHOR and MARINA studies were compared in terms of demographics and lesion characteristics, it was shown that older age, better initial VA, larger lesions, and larger abnormalities of retinal pigment epithelium were associated with VA loss[17-18]. Pushpoth *et al*[19] emphasised that maximum VA progression in patients with worse VA before treatment was hardly unexpected. Rasmussen *et al*[20] showed that initial worse VA and older age were related to worse final VA after a 4-year follow-up. They also reported that the VA value at the 3rd month was a stronger indicator for VA at 4y than the initial VA. In our study, we found that in patients with no previous treatment history, the VA progression was highest in Group 2. Reasons for this are likely to include the factors that Group 1 had relatively poor retinas and Group 3 suggested a ceiling effect. Additionally, Group 2 had more patients than the other groups. The visual outcomes in our study were similar to those in other studies with PRN regimens. After 3y, 81.1% of eyes showed no VA loss. Thus, the treatment stabilised the VA over the long term. For example, in HORIZON study, the VA in the 4th year was two letters more than the initial VA[21] and in SECURE study, after 3y, the VA was 4.3 letters less than the initial VA[22]. These VA changes were not statistically significant, so, again, the VA was essentially stable. In ANCHOR and MARINA studies, in which injections were performed monthly, after 2y the VA in 90% of the patients was stable.

Except for prospective studies there are few long-term studies about antiVEGF treatment in NV-AMD. In one of those studies, Berg et al. reported the 8-year-outcomes of intravitreal ranibizumab therapy with treat and extend modality in NV-AMD[6]. The 115 patients who were treated with bevacizumab initially were enrolled to this study and average BCVA change in comparison with first visit was investigated. Mean BCVA increased significantly in first year and by the end of 4th year BCVA was still significantly higher than onset. However, after 4y mean BCVA started to decline and at the end of 8y it was even under the initial value. Contributors explain the reason of this BCVA loss as macular atrophy. Since in the 5th year of the study macular atrophy in whole eyes was detected in FFA imaging. It was also pointed out that patients under follow-up by the end of 6th year were still under follow-up by the end of 8th year [40 of 115 patients (26%)]. Mean injection numbers were 6.1±2.8 and 5.4±3.5 during first and 8th years respectively. In 8th year of the study 87.5% eyes had stable neovascular lesions with no fluid in OCT. This study has one of the longest-term follow-up in NV-AMD and shows the effectiveness of ranibizumab with treat and extend modality during 4y. However mean BCVA in NV-AMD declines after 4y due to macular atrophy. In another recent and long-term study Ozkaya *et al*[7] reported 5-year outcomes of NV-AMD patients treated with ranibizumab with PRN regimen. In this single centered study, 44 eyes of 37 recently diagnosed and treated with only ranibizumab patients were enrolled. At the end of 5y mean BCVA was lower than first visit, 24 eyes (54.5%) lost 3 and more lines, 20 eyes (45.5%) had stable or improved BCVA. Average numbers of visits and injections were 25.3±5.3 and 12.6±6.4 respectively which are lower than prospective studies and reflects real-life results. Main outcome of this study was preserving BCVA in half of the patients after 5y with PRN ranibizumab therapy. However, in our study we accepted stable VA as ±1 line (5 letters) loss or gain. Whereas Ozkaya *et al*[7] took this limits ±3 lines in their study. Therefore our study seems more strict to say VA is stable. However 5-yeared real-life follow-up makes the study strong.

The largest clinical trials about the activity of most current antiVEGF “aflibercept” in NV-AMD are VEGF Trap-Eye Investigation of Efficacy and Safety in Wet AMD (VIEW) studies. VIEW1 and VIEW2 are similarly designed phase 3 studies. The efficacy of monthly and bimonthly intravitreal aflibercept injections were compared with monthly intravitreal ranibizumab injections. 2419 patients with CNVM secondary to AMD were enrolled to the study. Main outcome of the study was sustainability of VA (less than 15 letters loss) at 52nd week. In results, there were no significant difference between aflibercept and ranibizumab groups. According to BCVA change, morphological recovery and adverse events the outcomes were similar between the groups. After 3 loading doses, outcomes of each group were similar, which means aflibercept was effective in treatment of neovascular AMD with no doubt even performed bimonthly[8]. It is remarkable that main superiority of aflibercept is its therapeutic vigor with fewer injections. Because each injection brings not only financial burden but also ocular and systemical risks as haemmorage into vitreus, detechment of retina, elevated intraocular pressure, endophthalmitis, stroke and myocardial infarction. In the study showing the outcomes of 92wk of VIEW studies, the activity of aflibercept in exudative AMD after changing regimen in second year following a year with constant injection regimen was investigated. 2457 patients were enrolled to this study. Until 52nd week, after 3 loading injections monthly ranibizumab, monthly aflibercept and bimonthly aflibercept were performed. Between 52nd and 96th weeks original doses were performed with PRN regimen. At the end of this study it was reported that BCVA was preserved and VA of patients received 2 mg aflibercept bimonthly was similar to ranibizumab with 5 fewer injections[10]. The major outcome of this study is aflibercept can present VA loss with

fewer injections in long term. Again, in VIEW studies the upper limit of stable VA was 3 lines (15 letters) and different than our study. If the "preserved VA" limits of our study was accepted 3 lines as mentioned studies above, 90% of the eyes would have stable VA not only in short-term but also in long-term. Furthermore in VIEW studies injection regimen was constant and even with PRN the injections were performed at most once per 3mo.

In our study, at the end of 3y 24.7% of the eyes had gained >15 letters. In the CATT, ANCHOR, MARINA, and PrONTO studies this ratio was 30.7%, 41%, 33.3%, and 43%, respectively. At the end of 3y in our study, 90.1% of eyes showed a loss of not more than 15 letters or gained. This ratio was 97.5% in the PrONTO study and 96% in the study of Gupta *et al*[15]. In contrast to these prospective studies, in the study of Marques *et al*[23], which sought to reflect "real life" clinical practice, this ratio was 85%, which was similar to our result. In the same study, 13% of the eyes gained > 15 letters.

During the 36-month follow-up period, the average number of injections in our study was 7.3. Muniraju *et al*[24] reported an average of 10.2 injections at the end of 3y, Marques *et al*[23] reported an average of 8.4 injections at the end of 3y, and Pushpoth *et al*[19] reported an average of 8.2 injections at the end of 2y. In the PrONTO study, at the end of 2y, the average number of injections was 9.9. In comparison with these studies, we administered fewer injections. A likely explanation is that our injections were performed up to 2wk after the retreatment decision, not on the same day. Additionally, the expense of the medicine and patient pay periods may be another reason. These are the natural reflections of "real-life experience" and emphasized in some of the studies above as well[7,9].

According to similar studies, the general consensus is that the final VA shows no correlation with the average number of injections[20,24-27]. However, in Seven-Year Outcomes in Ranibizumab-Treated Patients in ANCHOR, MARINA, and HORIZON (SEVEN-UP) study, the average number of injections was 6.8 in 3.4y, but more VA progression was reported in the eyes that received at least 11 injections. Furthermore, it was reported that the visual outcomes in the eyes receiving fewer than five injections per year were poorer[28-29]. Similarly, Dodgostar *et al*[30] reported better visual outcomes with an increasing number of injections; however, the protocol in that study was PRN after just one loading injection. Thus, the difference may be due to the loading protocol. In our study, although there was a positive correlation between the final VA and the number of injections, it was not statistically significant. However, the power of the correlation did increase markedly with an extended follow-up period (Table 4).

A limitation of our study was that the VA measured at follow-up visits was not the best corrected VA. The reason, not surprisingly, was simply practical: congestion in our clinic. Also as a result of congestion, the injections could not be performed on the same day. Though there are differences between groups on the follow up duration was statistically significant, this is not the main aim of the study.

The strengths of this study include that it reflects real-life outcomes. Furthermore, in the literature, there are few reports about long-term outcomes of ranibizumab treatment in NV-AMD. After 3y of follow-up, in our NV-AMD patients treated with ranibizumab, VA progression was significant in those with mild initial VA (36-54 letters). Most eyes showed no VA loss regardless of the initial VA. We found no correlation between the final VA and the average number of ranibizumab injections.

ACKNOWLEDGEMENTS

Conflicts of Interest: Simsek B, None; **Ardagil Akcakaya A,** None; **Ozsoy Koyun I,** None; **Ari Yaylali S,** None.

REFERENCES

1 Wong TY, Wong T, Chakravarthy U, Klein R, Mitchell P, Zlateva G, Buggage R, Fahrbach K, Probst C, Sledge I. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. *Ophthalmology* 2008;115(1):116-126.

2 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.

3 Lindekleiv H, Erke MG. Projected prevalence of age-related macular degeneration in Scandinavia 2012-2040. *Acta Ophthalmol* 2013;91(4):307-311.

4 Brijesh T, Shorya A. Macular atrophy progression and 7-year vision outcomes in subjects from the ANCHOR, MARINA, and HORIZON studies: the SEVEN-UP study. *Am J Ophthalmol* 2016;162:200.

5 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.

6 Berg K, Roald AB, Navaratnam J, Bragadóttir R. An 8-year follow-up of anti-vascular endothelial growth factor treatment with a treat-and-extend modality for neovascular age-related macular degeneration. *Acta Ophthalmol* 2017;95(8):796-802.

7 Ozkaya A, Alkin Z, Togac M, Ahmet S, Perente I, Taskapili M. Five-year outcomes of ranibizumab in neovascular age-related macular degeneration: real life clinical experience. *Korean J Ophthalmol* 2017;31(5):424-430.

8 Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, Kirchhof B, Ho A, Ogura Y, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Soo Y, Anderesi M, Groetzbach G, Sommerauer B, Sandbrink R, Simader C, Schmidt-Erfurth U, VIEW and VIEW Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012;119(12):2537-2548.

9 Talks JS, Lotery AJ, Ghanchi F, Sivaprasad S, Johnston RL, Patel N, McKibbin M, Bailey C, Mahmood S, United Kingdom Aflibercept Users Group. First-year visual acuity outcomes of providing aflibercept according to the VIEW study protocol for age-related macular degeneration. *Ophthalmology* 2016;123(2):337-343.

10 Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, *et al*. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology* 2014;121(1):193-201.

11 Mitchell P, Korobelnik JF, Lanzetta P, Holz FG, Prunte 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.

12 Brown DM, Michels M, Kaiser 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.e5.

13 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.

14 CATT Research Group, 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.

15 Gupta OP, Shienbaum G, Patel AH, Fecarotta C, Kaiser RS, Regillo CD. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact. *Ophthalmology* 2010;117(11):2134-2140.

16 Brown DM, Tuomi, Shapiro H, Pier Study Group. Anatomical measures as predictors of visual outcomes in ranibizumab-treated eyes with neovascular age-related macular degeneration. *Retina* 2013;33(1):23-34.

17 Sadda SR, Stoller G, Boyer DS, Blodi BA, Shapiro H, Ianchulev T. Anatomical benefit from ranibizumab treatment of predominantly classic neovascular age-related macular degeneration in the 2-year anchor study. *Retina* 2010;30(9):1390-1399.

18 Rosenfeld PJ, Shapiro H, Tuomi, Webster M, Elledge J, Blodi B, MARINA and ANCHOR Study Groups. Characteristics of patients losing vision after 2 years of monthly dosing in the phase III ranibizumab clinical trials. *Ophthalmology* 2011;118(3):523-530.

19 Pushpoth S, Sykakis E, Merchant K, Browning AC, Gupta R, Talks SJ. Measuring the benefit of 4 years of intravitreal ranibizumab treatment for neovascular age-related macular degeneration. *Br J Ophthalmol* 2012;96(12):1469-1473.

20 Rasmussen A, Bloch SB, Fuchs J, Hansen LH, Larsen M, LaCour M, Lund-Andersen H, Sander B. A 4-year longitudinal study of 555 patients treated with ranibizumab for neovascular age-related macular degeneration. *Ophthalmology* 2013;120(12):2630-2636.

21 Singer MA, Awh CC, Sadda S, Freeman WR, Antoszyk AN, Wong P, Tuomi. HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology* 2012;119(6):1175-1183.

22 Silva R, Axer-Siegel R, Eldem B, Guymer R, Kirchhof B, Papp A, Seres A, Gekkieva M, Nieweg A, Pilz S, SECURE Study Group. The SECURE study: long-term safety of ranibizumab 0.5 mg in neovascular age-related macular degeneration. *Ophthalmology* 2013;120(1):130-139.

23 Marques IP, Fonseca P, Luz Cachulo M, Pires I, Figueira J, Faria de Abreu JR, Silva R. Treatment of exudative age-related macular degeneration with intravitreal ranibizumab in clinical practice: a 3-year follow-up. *Ophthalmologica* 2013;229(3):158-167.

24 Muniraju R, Ramu J, Sivaprasad S. Three-year visual outcome and injection frequency of intravitreal ranibizumab therapy for neovascular age-related macular degeneration. *Ophthalmologica* 2013;230(1):27-33.

25 Bandukwala T, Muni RH, Schwartz C, Eng KT, Kertes PJ. Effectiveness of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration in a Canadian retina practice: a retrospective review. *Can J Ophthalmol* 2010;45(6):590-595.

26 Arias L, Roman I, Masuet-Aumatell C, Rubio MJ, Caminal JM, Catala J, Pujol O. One-year results of a flexible regimen with ranibizumab therapy in macular degeneration: relationship with the number of injections. *Retina* 2011;31(7):1261-1267.

27 Hjelmqvist L, Lindberg C, Kanulf P, Dahlgren H, Johansson I, Siewert A. One-year outcomes using ranibizumab for neovascular age-related macular degeneration: results of a prospective and retrospective observational multicentre study. *J Ophthalmol* 2011;2011:405724.

28 Cohen SY, Dubois L, Tadayoni R, Fajnkuchen F, Nghiem-Buffet S, Delahaye-Mazza C, Guiberteau B, Quentel G. Results of one-year's treatment with ranibizumab for exudative age-related macular degeneration in a clinical setting. *Am J Ophthalmol* 2009;148(3):409-413.e1.

29 Brown DM, Regillo CD. Anti-VEGF agents in the treatment of neovascular age-related macular degeneration: applying clinical trial results to the treatment of everyday patients. *Am J Ophthalmol* 2007;144(4):627-637.

30 Dadgostar H, Ventura AA, Chung JY, Sharma S, Kaiser PK. Evaluation of injection frequency and visual acuity outcomes for ranibizumab monotherapy in exudative age-related macular degeneration. *Ophthalmology* 2009;116(9):1740-1747.