European Journal of Ophthalmology

# ACCESSIBILITY AS A CONDITIONING FACTOR IN TREATMENT FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION

--Manuscript Draft--

| | |
|---|---|
| **Manuscript Number:** | EJO-D-13-00210 |
| **Full Title:** | ACCESSIBILITY AS A CONDITIONING FACTOR IN TREATMENT FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION |
| **Short Title:** | ACCESSIBILITY TO TREATMENT IN AGE-RELATED MACULAR DEGENERATION |
| **Article Type:** | Original Article |
| **Section/Category:** | Socioeconomics and Education medicine/ophthalmology |
| **Keywords:** | Bevacizumab,Cohort Studies, Health Services Accessibility, Macular Degeneration, Ranibizumab, Effectiveness |
| **Corresponding Author:** | Gladys E. Granero<br>Faculty of Chemical Sciences-National University of Córdoba. Argentina<br>Córdoba, Cordoba ARGENTINA |
| **Corresponding Author's Institution:** | Faculty of Chemical Sciences-National University of Córdoba. Argentina |
| **First Author:** | Juan Pablo Real |
| **Order of Authors:** | Juan Pablo Real |
| | José D. Luna |
| | Julio A. Urrets-Zavalia |
| | Mariana O. De Santis |
| | Santiago D. Palma |
| | Gladys E. Granero |
| **Manuscript Region of Origin:** | ARGENTINA |
| **Abstract:** | Purpose: Ranibizumab and Bevacizumab, coexist as the main therapeutic strategies for the treatment of neovascular-age-macular-degeneration (NV-AMD). In Argentina the access pathways both drug are completely different. Patients with different pathways and gatekeepers to access may experience different outcomes. The purpose of this work was to estimate the impact on therapeutic effects and visual outcome of the different accessibilities to NV-AMD treatment.<br><br>Methods: A retrospective analysis of the charts of 78 patients with previously untreated exudative AMD, who were treated with Ranibizumab or Bevacizumab between January 2009 and December 2011, was conducted. The main outcomes measured included time delay and change in mean best-corrected-visual-acuity (BCVA) between diagnosis and treatment and mean BCVA change at 1 year follow-ups.<br>Results: The delay between diagnosis and treatment and decrease in visual acuity over this time was significantly higher for patients treated with Ranibizumab. At 1 year after the initiation of treatment, BCVA had a mean increase from baseline of 0.11 letters in the Bevacizumab-group with a mean of 4.71 injections, compared with a decrease of 8.87 letters with a mean of 2.98 injections in the Ranibizumab-group.<br>Conclusions: The access to treatment can be a key factor for success of therapy. Waiting times and availability of doses are crucial in the treatment of NV-AMD. More important than define whether Bevacizumab or Ranibizumab is used. |
| **Suggested Reviewers:** | R. Borrone, Dr.<br>Department of Ophthalmology, Retina Center, Diabetes Section, University of Buenos Aires, School of Medicine, Buenos Aires<br>rborrone@intramed.net.ar |
| **Opposed Reviewers:** | GC ..Rossi , Dr.<br>.University Eye Clinic of Pavia, IRCCS Policlinico San Matteo Foundation, Pavia, Italy |

| | |
|---|---|
| | gemma.rossi.md@gmail.com |
| **Additional Information:** | |
| **Question** | **Response** |
| Financial support: indicate grants and funds in support of the Study. If none, please state so. | No financial support was received for this submission |
| Meeting Presentation: state if the manuscript was presented at a meeting, its name, place and date on which it was read. | Some aspect of this paper were presented orally in the IX National Congress of the Association for Research in Vision and Ophthalmology (AIVO 2012) and in the 2nd International Meeting on Pharmaceutical Sciences (RICIFA 2012) in November of 2012. |
| Informed Consent: in case of manuscripts reporting the results of experimental investigation on human subjects, human derived material or human medical records include a statement that the study was performed with informed consent and following all the guidelines for experimental investigations required by the Institutional Review Board or Ethics Committee of which all authors are affiliated. | Our study complied with the Helsinki declaration and the law 25326/2000 "Protection of Personal Data" that ensures the confidentiality of information obtained and the identity of patients involved. This study has been approved by Institutional ethics committee of the National Clinical Hospital coordinated by Dr Hilda Montrull. It has been registered in the Register Provincial Health Research (REPIS) under number 059/10 |
| Proprietary Interest: state whether any Author(s) have proprietary interest in the manuscript or not. | Authors have not proprietary interest in the manuscript |
| If your manuscript has been previously rejected by another publication please inform the Journal indicating how the manuscript has been improved according to the reviewers comments received. | The manuscript has been evaluated and has been denied publication in British Journal of Ophthalmology.There are no comments for the authors since it is the decision of the Editorial Board |

# ACCESSIBILITY AS A CONDITIONING FACTOR IN TREATMENT FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION

**Short title: ACCESSIBILITY TO TREATMENT IN AGE-RELATED MACULAR DEGENERATION**

Juan P. Real[a], José D. Luna[b], Julio A. Urrets-Zavalia[c], Mariana O. De Santis[d], Santiago D. Palma[a] and Gladys E. Granero[a]*

[a]From Pharmacy Departament of the Faculty of Chemical Sciences. National University of Córdoba. Argentina. UNITEFA (CONICET).

[b] From Vitreo-retinal department, Centro Privado de Ojos Romagosa SA - Fundación VER, Córdoba, Argentina.

[c] From Department of Ophthalmology, University Clinic Reina Fabiola, Catholic University of Córdoba, Argentina.

[d]From Institute of Economics and Finance, School of Economics Sciences, National University of Córdoba. Argentina.

* Gladys E. Granero. Pharmacy Departament of the Faculty of Chemical Sciences. National University of Córdoba, Argentina. Haya de la Torre y Medina Allende. Ciudad Universitaria Edificio Ciencias II, X5000HUA - Córdoba - Argentina - TE/Fax: +54 351 5353865-53356. E-mail: glagra@fcq.unc.edu.ar

**Conflict of interest:** None of the authors has conflict of interest with the submission

**Financial support:** No financial support was received for this submission

**Abstract**

**Purpose:** Ranibizumab and Bevacizumab, coexist as the main therapeutic strategies for the treatment of neovascular-age-macular-degeneration (NV-AMD). In Argentina the access pathways both drug are completely different. Patients with different pathways and gatekeepers to access may experience different outcomes. The purpose of this work was to estimate the impact on therapeutic effects and visual outcome of the different accessibilities to NV-AMD treatment.

**Methods**: A retrospective analysis of the charts of 78 patients with previously untreated exudative AMD, who were treated with Ranibizumab or Bevacizumab between January 2009 and December 2011, was conducted. The main outcomes measured included time delay and change in mean best-corrected-visual-acuity (BCVA) between diagnosis and treatment and mean BCVA change at 1 year follow-ups.

**Results:** The delay between diagnosis and treatment and decrease in visual acuity over this time was significantly higher for patients treated with Ranibizumab. At 1 year after the initiation of treatment, BCVA had a mean increase from baseline of 0.11 letters in the Bevacizumab-group with a mean of 4.71 injections, compared with a decrease of 8.87 letters with a mean of 2.98 injections in the Ranibizumab-group.

**Conclusions**: The access to treatment can be a key factor for success of therapy. Waiting times and availability of doses are crucial in the treatment of

NV-AMD. More important than define whether Bevacizumab or Ranibizumab is used.

**Keywords**: Bevacizumab, Cohort Studies, Health Services Accessibility, Macular Degeneration, Ranibizumab.

## INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of severe visual loss in the developed world, and its neovascular complications (neovascular AMD or NV-AMD) are responsible for the majority of this visual loss. [1] The introduction of anti-vascular endothelial growth factor (VEGF) therapy has changed the treatment of NV-AMD and has become a standard treatment for NV- AMD. [2-3]

Currently, the two most commonly used VEGF antagonists are ranibizumab (Lucentis; Genentech, San Francisco, California, USA) and bevacizumab (Avastin; Genentech). Both these molecules are derived from the same murine monoclonal antibody against VEGF. Ranibizumab was specifically designed and approved for the intravitreal treatment of exudative AMD, and bevacizumab was approved for the systemic intravenous treatment of metastatic colorectal cancers. Nevertheless, this anti-angiogenic monoclonal antibody is not currently FDA approved for injection into the eye, although the efficacy and tolerability of intravitreal bevacizumab has been reported by hundreds of articles. [4-10] In fact, it is nowadays used off-label not only for the treatment of exudative AMD but also for other ischemic retinopathies. [11-12]

The comparison of AMD Treatments Trials (CATT), (a randomized and prospective trial comparing ranibizumab with bevacizumab), has shown that both anti-VEGF agents had equivalent effects on visual acuity when administered according to the same schedule [4-5].However, due to the cost savings from the use of bevacizumab, along with the perception that

bevacizumab and ranibizumab are similar with respect to safety and efficacy, the global off-label use of Bevacizumab is far more common. [13]

In Argentina, as in many countries, RNB and BVZ, coexist as the main therapeutic strategies for the treatment of macular degeneration, with the peculiarity that in this country the access pathways both drug are completely different.

The first case, RNB is recognized both by health authorities as well as many health insurances. Although the treatment is usually covered, the high cost of the treatment causes this medical insurances to demand a revision of each case individually, which requires the fulfillment of a series of administrative procedures and studies that requires organization, self-commitment and mobility, turning it into a very complicated task considering that we are talking about elderly patients.

Since the beginning of the treatment without the approval of the medical insurance involves a significant financial risk to the patient, the initiation of treatment is delayed.

For his part, BVZ, when used off label, is not recognized by the health insurance systems. It must be paid in full by the patient who is confronted with the decision of choosing between paying for a medicine without formal recognition but which would allow a faster access to the treatment.

On the other hand the total number of doses will be limited by the number delivered by the patient’s medical insurance or by the patient's willingness to pay.

If we finally consider that these treatments only slow the progression and reactivation of the disease and that the damage caused can be irreversible, the delay in the initiation of the treatment and the number of doses available, considered as accessibility, are factors that can clearly influence the effectiveness of treatments. So, patients with different pathways may have different delays and, therefore, better or worse prognosis. Our objective was to evaluate the impact on therapeutic effects and visual outcome of the different accessibilities to neovascular AMD treatment.

## METHODS

The design of the study was a retrospective cohort study based on analysis of clinical charts and complementary studies of all patients treated with ranibizumab (Lucentis®) or bevacizumab (Avastin®) at three of the major ophthalmological centers of Córdoba, Argentina, (Department of Ophthalmology, National Hospital of Clinics, National University of Córdoba; Centro Privado de Ojos Romagosa-Fundación VER and Department Ophthalmology, University Clinic Reina Fabiola, Catholic University of Córdoba) from January 2009 to December 2011.

**Patients:** The inclusion criteria consisted of charts of patients aged over 50 years with treatment-naïve subfoveal CNV secondary to neovascular AMD, confirmed by intravenous fluorescein angiogram (FA) or optical coherence tomography (OCT), who were managed with intravitreal bevacizumab or ranibizumab in one of three ophthalmologic centers.

Charts of patients with choroidal neovascularization related to degenerative myopia, angioid streaks, chorioretinal inflammatory diseases, hereditary retinal disorders, or central serous chorioretinopathy were excluded from the analysis, as well as those with CNV secondary to polypoidal choroidal vasculopathy or retinal angiomatous proliferation, or with a history of laser photocoagulation treatment, verteporfin photodynamic therapy (PDT) or prior intravitreal therapy. Patients that during the monitoring year had received a combined treatment with other intravitreal drugs and / or surgical treatments that could have modified the visual acuity, such as phacoemulsification, were also excluded.

**Collecting Data:** The assignment of patients and treatment regimen was not controlled by researchers. Information gathered from the patient´s baseline visit included their age at presentation, gender, time elapsed from the beginning of symptoms, and which eye was involved, best-corrected visual acuity (BCVA), the presence or absence of cataracts, intraocular pressure, type of choroidal neovascularization, optical coherence tomography (OCT) and FA pretreatment findings, ocular history, and date.

At each follow-up visit, data about patients´ best-corrected visual acuity, fundus biomicroscopic findings, OCT measurements and characteristics, FA findings, adverse ocular and non-ocular events and the date of visit were collected.

BCVA was recorded for all chart´s patients by using the best-corrected distance Snellen chart and converting this by taking the logarithm of minimum angle of resolution (logMAR) units where a logMAR unit = -log10[Snellen vision

fraction]. The differences in visual acuity were expressed in letters (each letter having a score value of 0.02 log units)

**Ethical Considerations:** Our study complied with the Helsinki declaration and the law 25326/2000 "Protection of Personal Data" that ensures the confidentiality of information obtained and the identity of patients involved. This study has been approved by Institutional ethics committee of the National Clinical Hospital coordinated by Dr Hilda Montrull. It has been registered in the Register Provincial Health Research (REPIS) under number 059/10

**Outcomes:** Six time points were used for analysis: baseline (diagnostic visit), diagnostic confirmation (by a OCT and/or FA), initiation (first injection), 3 months, 6 months, and 1 year.

From these follow-up data, the necessary information was obtained to compare:

**The waiting time and change in visual acuity**: The waiting time was defined as the period of time between the patient first ophthalmological consultation with macular visual symptoms and the date of therapy initiation.

Change in visual acuity over waiting time was measured as the visual acuity score at the initiation of the therapy date minus the visual acuity score at the diagnosis visit. BCVA was expressed as logMAR and an unpaired Student´s t-test was used to evaluate differences between groups in BCVA outcomes.

**Doses and follow-up examinations:** An analysis was made by comparing the proportion of patients who received a minimum of 3 doses, the proportion of patients who received additional doses and the mean number of clinical evaluations and doses received for both cohorts within a year of treatment.

**The impact of initiation of treatment on the BCVA**: It was evaluated by comparing the BCVA at 3 month, 6 month and 12 month intervals after therapy initiation. Changes in logMAR acuity within groups were compared by means of a paired Student´s test and between groups with an unpaired Student´s t-test.

**Effectiveness of treatments:** The overall treatment effect was assessed by comparing the BCVA of the baseline with that at follow-up periods. The primary outcome was the change in visual acuity. The secondary outcomes included the proportion of patients with a change in BCVA of 0.3 LogMar (15 letters) or more and the proportion of patients with a change in BCVA of fewer than15 letters. .

**Statistical method:** All statistical analyses were performed using SPSS package for Windows (version 16.0, SPSS Inc., Chicago, IL). Absolute and relative frequencies were used for qualitative variables with means and standard deviations being used to summarize quantitative data. The normal distribution of data was tested using the Shapiro-Wilk test. Quantitative

variables were compared using a Student's test for unpaired samples and a non-parametric Wilcoxon Man-Whitney test if the variables did not meet the normality criteria. For comparisons of proportions, a Fisher-Irwin Test was used. The statistical relationship between the variables was analyzed by means of the Pearson's correlation test as well as multiple linear regression analysis. A P-value of 0.05 or less was considered to be statistically significant.

## RESULTS

From January 2009 to December of 2011, a total of 128 eyes were consistent with the diagnosis of AMD and 96 eyes met the inclusion and exclusion criteria. In addition 52 eyes (41 patients) were treated with bevacizumab and 44 eyes (37 patients) with ranibizumab. Table 1 shows the baseline characteristics of both groups. There were no statistically significant differences between groups in terms of gender distribution or CNV characteristics. However, there was a statistically significant difference between groups with regards of age, the oldest being the ranibizumab one (Table 1).

**The total waiting time and change in visual acuity**:

The average waiting time was found to be 36.06 days (SD 21.86 days, IC: 29.97- 42.14 days) for the bevacizumab group and 153.80 days (SD 76.36 days, IC: 130.58-177.01 days) for the ranibizumab group. The differences between groups were statistical significant ($p < 0.0001$). The diagnostic confirmation time (defined as elapsed time between baseline date and diagnostic confirmation date) was 19.21 days (SD 14.96 days, IC: 15.05-23.38

days) for the bevacizumab group and 28.4 days (SD 27.66 days, IC: 20.00-36.86 days) for the ranibizumab group, a difference that however did not reach statistical significance (p = 0.053).

During waiting time, the BCVA of patients from both groups decreased from 0.80 (SD 0.43) logMAR to 0.91 (SD 0.44) logMAR for the bevacizumab group, and from 0.77 (SD 0.39) logMAR to 1.03 (SD 0.4) logMAR for the ranibizumab group.

An indirect association between this changes in BCVA and waiting time was found (Pearson coefficient -0.41 p value <0.001), implying that the higher the delay from diagnosis time to treatment the less likely the visual acuity will improve after treatment charging state, regardless of the evaluated cohort. Both groups showed a statistically significant reduction in BCVA (p <0.01), being significantly higher (p <0.01) in the group treated with ranibizumab which lost an average of -13.01 letters (SD 13.82 ), in comparison with the bevacizumab group which lost -5.46 letters (SD 9.90).

**Doses and follow-up examinations:**

After one year of follow-up periods, it was found that 96% (IC: 87-100%) and 91% (IC: 78-97%) of patients from the bevacizumab and ranibizumab groups, respectively, received at least 3 doses of the corresponding anti-VEGF agent. The mean time to having 3 administered doses was 71.27 days (SD 23.42 days, IC: 64.54-77.99 days)) for the bevacizumab group and 78.93 days (SD 34.84 days, IC: 67.78-90.07 days) for the ranibizumab group. No

statistically significant differences between groups were found for the above mentioned parameters.

With regard to the maintenance phase or retreatment, in the ranibizumab group only 25 % (IC: 13-40%) of eyes received additional doses to those given after the loading dose phase, while in the bevacizumab group this occurred in 92% (IC: 81-98%) of cases ($p < 0.0001$). Thus, the average total number of doses for a one- year follow-up period in each group was 4.71 (SD 1.45, IC: 4.31-5.11) and 2.98 (SD 0.55, IC: 2.81-3.14) for the bevacizumab and ranibizumab groups, respectively ($p < 0.0001$).

The average number of clinical evaluations during a 1 year of follow-up period for the bevacizumab group was 8.23 (SD 2.65) and was 9.66 (SD 3.26) for the ranibizumab group (p value <0, 0001). Also there existed a significant decrease (p value <0, 0001) of consultation numbers occurring in the second half of the follow-up period. The clinical evaluations decreased from an average of 5.62(SD 1.78) for the bevacizumab groups and of 7.09 (SD 2.45) for the ranibizumab group, in the first half of the year, to 2.62 (SD 1.79) and 2.57 (SD 2.12) in the second half for the bevacizumab and ranibizumab groups, respectively (p value <0, 0001).

**The impact of initiation of treatment on the BCVA:**

After treatment initiation, there was a significant visual acuity improvement in both groups ($p < 0.05$) (Figure 1). At 3, 6 and 12 month follow-up periods, the improvement in visual acuity was 10.06, 8.24 and 6.27 letters for

the bevacizumab group and 6.27, 6.61 and 3.37 letters for the ranibizumab group. Differences between groups were not statistically significant (p= 0.097).

Both groups showed a drop in visual acuity in the period between the 6 month and 12 month follow-ups after treatment initiation (Figure 1). Globally, the BCVA decreased from 0.81 logMAR at 6 moth follow-up period to 0.86 logMAR at 12 months follow-up period, which was statistically significant (p< 0.05).

**Effectiveness of treatments:**

Regarding BCVA changes from baseline to the 6 months follow-up period, an average increase of +2.79 letters occurred in the bevacizumab group. In contrast, patients from the ranibizumab group lost 6.4 letters. After the 1 year follow-up, the overall average visual change in the bevacizumab group was of 0.11 letters compared with -8.9 letters for patients of the ranibizumab group (p=0.038) (Figure 2).

The proportion of patients who did not experience a decrease in visual acuity of 3 or more lines on the Snellen chart report card or more, from diagnostic confirmation date (baseline) to the 6 month and 12 month follow-up periods, was of 90% and 80%, respectively, for the bevacizumab group, while these values were of 64% and 56% , respectively, for the ranibizumab group (Table 2).

**DISCUSSION**

The data analysis from our study showed that a delayed initiation of therapy of an average of 36.06 days was enough to produce a significantly unfavorable change in visual acuity (loss of more than 1 line on the Snellen chart). These data are consistent with findings obtained by Muether et al. [14]., who concluded that a waiting time of 4 weeks for therapy initiation after diagnosis of exudative AMD produced adverse change to the vision.

It was found that the proportion of patients that lost more than 15 letters increased significantly with increasing time delay for treatment initiation after initial symptoms, i.e. from 21% for 36 days of delay to 43% when the delay time was of ~5 months had been observed

When considering the visual acuity change from the Initiation to 12 months of follow-up, there was a tendency to achieve a better response to therapy in patients treated with bevacizumab, even though statistical significance was not obtained between the two groups.

In both groups, it was observed that the number of follow-up visits and injections over the first year occurred less frequently than those in the CATT-study-as-needed groups [4, 5]. Even though there are not differences in the percentage of patients that complete the loading phase, the yearly mean injection rate in the ranibizumab group was statistically smaller than that of the bevacizumab group ($p < 0,0001$). This may have been also associated with barriers in the access of doses. The lower number of injections and visits over the course of the first year of follow-up, for both studied groups, could be associated with deterioration in visual acuity from month 3 to month12 of the follow-up period. The improvement in visual acuity obtained in the loading

phase, decreased during this follow-up period, and at month 12 the mean visual acuity was equal or worse than initial values. These findings agree with other reported observational studies, where the visual acuity of the loading phase could not be improved or even conserved until month 12 [15, 16]. Thus, the very impressive visual improvement and stabilization observed in phase III trials with monthly injections of ranibizumab may not reflect the outcomes in current clinical practices.

Regarding the change in visual acuity from the baseline to 12 months of follow-up, which is a measure of the overall influence of all the variables described, the study revealed a significantly better result in the bevacizumab group than in the ranibizumab group. After a one-year follow-up the RNB group obtained similar results to those of the placebo groups of clinical trials. The group treated with BVZ achieved inferior results to those achieved in clinical trials but similar to those obtained by RNB patients in routine clinical practice of other health systems (Table 3).

These results show that the medicine with higher cost for the health system (Ranibizumab) is the one that obtains worse results, and not for being less effective, but because exists restrictions that delay the access to the doses.

In conclusion, waiting times and availability of doses are crucial in the treatment of neovascular AMD, and the barriers to access for treatment may limit the possibility of patients preserving their vision. Non-clinical factors, such as accessibility and cost of treatment, influence the effectiveness of therapy especially if resources are scarce.

Apparently, solving the problems related to delayed initiation of therapy and the difficulties in the maintenance phase (such as poor adherence to monitoring visits or barriers in access to maintenance doses) are more important than define whether Bevacizumab or Ranibizumab is used.

## REFERENCES


1) Resnikoff S, Pascolini D, Etya'ale D et.al. Global data on visual impairment in the year 2002. Bull World Health Organ. 2004 Nov;82(11):844-51

2) Rosenfeld PJ, Brown DM, HeierJS, et al, for the MARINA Study Group. Ranibizumab For neovascular agerelated macular degeneration. N Engl J Med. 2006;355(14):1419-1431.

3) Brown DM, Kaiser PK, Michels M, et al, for the ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1432-1444

4) CATT Research Group; Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age related macular degeneration. N Engl J Med 2011;364(20):1897–1908

5) CATT Research Group, Martin DF, Maguire MG, Fine SL, Ying GS, et al. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration:Two-Year Results. Ophthalmology. 2012 Jul;119(7):1388-98.

6) Schouten JS, La Heij EC, Webers CA, et.al. A systematic review on the effect of bevacizumab in exudative age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2009 Jan;247(1):1-11

7) Ziad F. Bashshur, MD; Alexandre Schakal, MD; Rola N, et.al. Intravitreal Bevacizumab vs Verteporfin Photodynamic Therapy for Neovascular

Age-Related Macular Degeneration. Arch Ophthalmol. 2007;125(10):1357-136.

8) Weigert G, Michels S, Sacu S, et al. Intravitreal bevacizumab (Avastin) therapy versus photodynamic therapy plus intravitreal triamcinolone for neovascular age-related macular degeneration: 6-month results of a prospective, randomised, controlled clinical study. Br J Ophthalmol. 2008 Mar;92(3):356-60

9) Sacu S, Michels S, Prager F, et al. Randomised clinical trial of intravitreal Avastin vs photodynamic therapy and intravitreal triamcinolone: long-term results. Eye 2009; 23:2223-7.

10) Tufail A, Patel PJ, Egan C, et al; ABC Trial Investigators. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. BMJ. 2010 Jun 9;340:c2459.

11) Vasudev D, Blair MP, Galasso J, et al. Intravitreal bevacizumab for neovascular glaucoma. J Ocul Pharmacol Ther. 2009 Oct;25(5):453-8.

12) Lynch SS, Cheng CM. Bevacizumab for neovascular ocular diseases. Ann Pharmacother. 2007 Apr;41(4):614-25.

13) Gonzalez S, Rosenfeld PJ, Stewart MW, et al.. Avastin doesn't blind people, people blind people. Am J Ophthalmol. 2012 Feb;153(2):196-203

14) Muether PS, Hermann MM, Koch K, et al .Delay between medical indication to anti-VEGF treatment in age-related macular degeneration can result in a loss of visual acuity. Graefes Arch Clin Exp Ophthalmol. 2011 May;249(5):633-7.

15)Bandukwala T, Muni RH, Schwartz C, et al. Effectiveness of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration in a Canadian retinapractice: a retrospective review. Can J Ophthalmol. 2010 Dec;45(6):590-5.

16)Cohen SY, Dubois L, Tadayoni R, et al. Results of one-year's treatment with ranibizumab for exudative age-related macular degeneration in a clinical setting. Am J Ophthalmol. 2009 Sep;148(3):409-13.

17)Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) Study Group. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials--TAP report. Arch Ophthalmol. 1999 Oct;117(10):1329-45

**‘TITLES AND LEGENDS TO FIGURES’**

**FIGURE 1**:

Mean change in visual acuity letter scores from the first injection of the anti-VEGF agent (treatment initiation) to month 12 of follow-up.

**FIGURE 2**:

(a) Mean change in visual acuity letter scores from baseline to month 12 of follow up.

(b):

- The Percentage of patients who had decreased BCVA of 0.3 LogMar (15 letters) or more from baseline to month 12 of follow up.
- The Percentage of patients who had a change in their BCVA less than 0.3 LogMar (15 letters), from baseline to month 12 of follow up.
- The Percentage of patients who had increased their BCVA of 0.3 LogMar (15 letters) or more from baseline to month 12 of follow up.

BVZ= Bevacizumab; RNB= Ranibizumab

**TABLE 1. Comparison of Baseline Characteristics between Ranibizumab and Bevacizumab Groups**

| Baseline Caracteristics | Bevacizumab | Ranibizumab | p value |
|---|---|---|---|
| **Number of case** | 52 | 44 | |
| **Male, n (%)** | 17(33%) | 17(39%) | 0.66 |
| **Female, n (%)** | 35(77%) | 27(61%) | 0.66 |
| **Age Mean (SD)** | 73.9(9.28) | 78.64(6.76) | **<0.01** |
| **Occult CNV lesion n (%)** | 22(44%) | 17(13%) | 0.83 |
| **Classic CNV lesion n (%)** | 19(28%) | 18(29%) | 0.68 |
| **Unknown/not stated of CNV lesion n (%)** | 11(28%) | 9(58%) | 0.99 |
| **VA ≥20/40 n (%)** | 8(15%) | 6(13%) | 0.99 |
| **20/40 >VA >20/320 n (%)** | 32(62%) | 31(70%) | 0.39 |
| **VA ≤20/320 n (%)** | 12(23%) | 7(16%) | 0.45 |
| **Mean VA all case (LogMar)** | 0.79(0.42) | 0.77(0.39) | 0.8 |
| **Pseudophakic cases** | 16(31%) | 15(34%) | 0.82 |
| **Cases with Glaucoma** | 8(15%) | 4(9%) | 0.38 |
| **Cases with Systemic hypertension** | 29(56%) | 20(45%) | 0.41 |

**CNV =choroidal neovascularization; SD=standard deviation; VA =visual acuity**

**TABLE 2: Clinical Outcomes at different times**

| Outcome | Time point | Bevacizumab (all eyes) | Ranibizumab (all eyes) | p value |
|---|---|---|---|---|
| **Mean Change in VA Score from baseline (LogMAR letters)** | **Initiation** | -5.46 (SD:9.9) | -13.01 (SD:13.82) | **0,003** |
| | **3 months** | 4.61 (SD:13.61) | -6.74 (SD:16.73) | **<0.001** |
| | **6 months** | 2.79 (SD:13.78) | -6.4 (SD:19.36) | **0,01** |
| | **12 months** | 0.11 (SD:17.05) | -8.87 (SD:20.68) | **0,038** |
| **% Cases that lost <=15 letters (Nº cases)** | **Initiation** | 81% (42) | 57% (25) | **0,01** |
| | **3 months** | 92% (48) | 64% (28) | **<0.01** |
| | **6 months** | 90% (47) | 64% (28) | **<0.01** |
| | **12 months** | 80% (32) | 56% (22) | **0,03** |
| **% Cases that gained >=15 letters (Nº cases)** | **Initiation** | - | - | - |
| | **3 months** | 21% (11) | 7% (3) | 0,08 |
| | **6 months** | 17% (9) | 14% (6) | 0,8 |
| | **12 months** | 18% (7) | 10% (4) | 0,5 |

**LogMAR= logarithm of the Minimum Angle of Resolution; SD=standard deviation; VA =visual acuity; Initiation=first injection visit; 3 months, 6 months, 12 months= visit closest to 90, 183, and 365 days from first injection**

**Table 3**

**Comparison of the Clinical Outcomes of this study with those of placebo groups, CATT trial and of two retrospective studies conducted in others countries.**

| Clinical Outcome | Clinical Trials | | | | Observacional Study | | Our Study | |
|---|---|---|---|---|---|---|---|---|
| | MARINA (2006), Sham injection [2] | TAP (2001), Placebo [17] | CATT (2011), RNB PRN [7] | CATT (2011), BVZ PRN [7] | Cohen et. al (2009), RNB [15] | Bandukwala (2010), RNB [16] | Our Study (2012). BVZ | Our Study (2012) RNB |
| Mean Change in VA[a)] | -10,4 | -4,5 | 6,8 | 5,9 | 0,7 | 2,88 | 0,11 | -8,87 |
| % who lost <15 letters [b)] | 62,20% | 46,30% | 91,50% | 95,40% | 90,30% | 82,00% | 80,00% | 56,00 % |
| % who gained $\geq$ 15 letters [c)] | 10,90% | 2,40% | 25,00% | 28,00% | 8% | 25% | 18,00% | 10,00 % |

**RNB=Ranibizumab; BVZ=Bevacizumab; PRN=Pro re nata**

a) Mean Change in Visual-Acuity Score from baseline to month 12 of follow up (no. of letters)

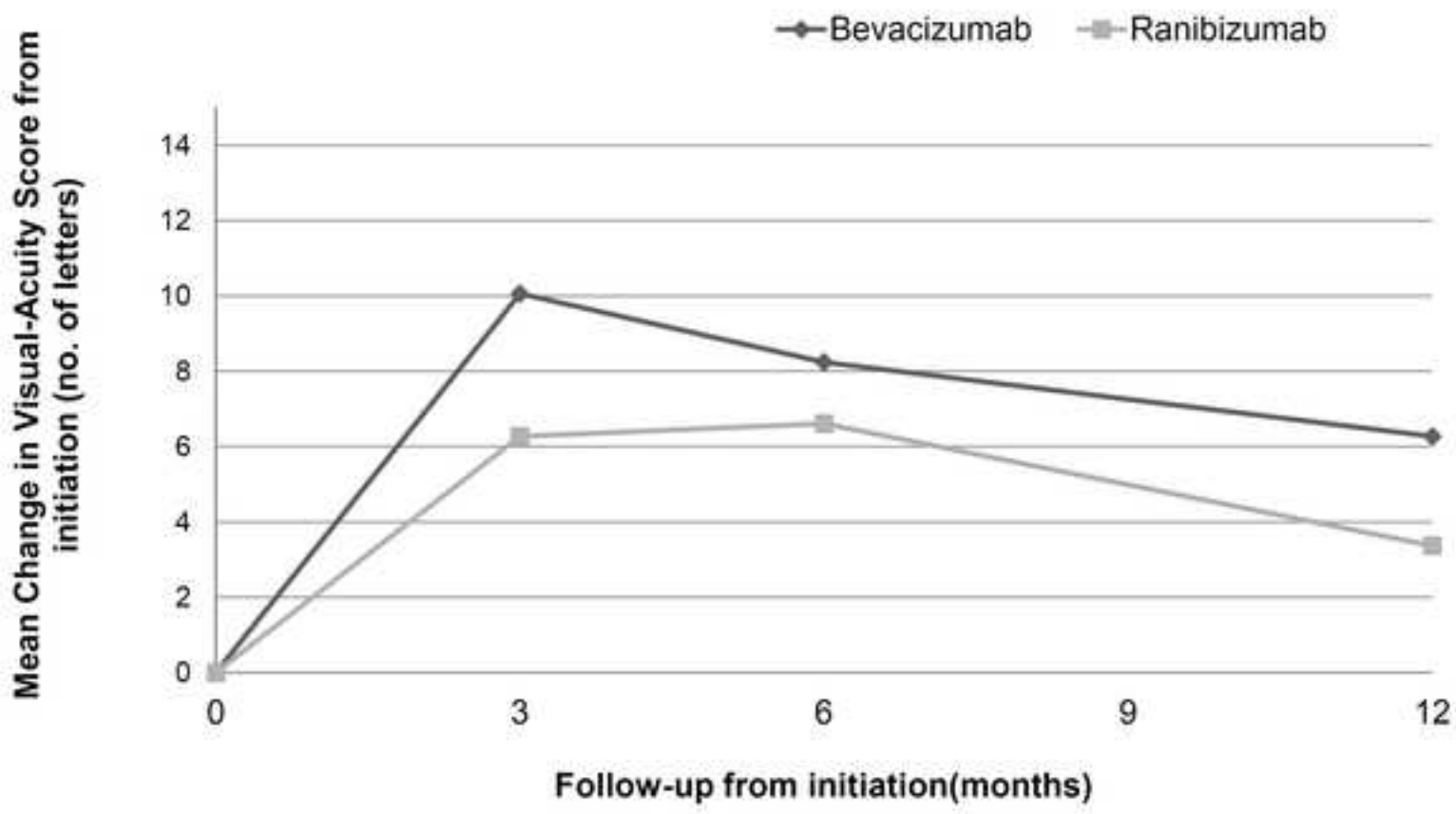
b) The Percentage of patients in each group who lost fewer than 15 letters from baseline visual acuity at 12 months

c) The percentage of patients who gained 15 or more letters from baseline at 12 months

## SUMMARY STATEMENT

Retrospective cohort study based on analysis of clinical charts and complementary studies of patients who were treated with RNB or BVZ for AMD-NV was conducted to evaluate different accessibility to neovascular AMD treatment in clinical practice and estimate its impact in therapeutic effects and visual outcome. These results show that the differences in accessibility of treatment are factors that can clearly influence the effectiveness of treatments. Off-label bevacizumab appears as an option to achieve better results, not related to the drug´s efficacy itself but because of the difference in restrictions of time and number when a dose is required

Figure
Click here to download high resolution image




| Mean Change (SD) in Visual-Acuity Score from initiation (no. of letters) | 3 months | 6 months | 12 months |
|---|---|---|---|
| Bevacizumab group | +10.06 (12.97) | +8.24 (13.01) | +6.27 (17.63) |
| Ranibizumab group | + 6.27 ( 9.05) | +6.61 (13.85) | +3.37 (14.97) |
| p value | 0.097 | 0.552 | 0.433 |

Figure
Click here to download high resolution image