Ranibizumab Monotherapy in Neovascular Age-Related Macular Degeneration with Pigment Epithelial Detachment

Abumere Akinwale, Moss Fenberg, Vanessa Vasquez and Deeba Husain*

Retina Service, Department of Ophthalmology, Boston University school of Medicine, 85 east concord street, 8th floor, Boston MA 02118, USA

Abstract

Purpose: To evaluate the effect of ranibizumab monotherapy in patients with neovascular age related macular degeneration (AMD) associated with a pigment epithelial detachment (PED).

Methods: A retrospective chart review of neovascular AMD with associated PED treated using initial three monthly doses of ranibizumab followed by as needed dosing. The response to treatment was assessed by evaluating changes in visual acuity and central macular thickness (CMT) by ocular coherence tomography. The total ranibizumab injections needed was also assessed.

Results: A total of 14 eyes from 12 patients were included in this study. The average follow up period was 35 months (range 17 - 62 months). The mean logMAR visual acuity decreased from 0.596 (snellen ~20/80) to 1.018 (snellen ~20/200), however this was not statistically significant (p=0.05). The mean central macular thickness (CMT) also decreased from initial CMT 288 to final CMT 277.08. There was no statistically significant difference between the initial and final CMT (p=0.80). An average of 10 ranibizumab injections per eye (range 3-23 injections) was administered over the duration of the study.

Conclusions: Our pilot study suggests that ranibizumab monotherapy administered on an as needed basis, in cases of patients with neovascular AMD with PED may be of questionable benefit. The treatment modality appeared to be ineffective in improving visual acuity as well as CMT. Combined treatment approaches may be necessary at an early stage to prevent visual loss in these cases.

Introduction

Age-related macular degeneration (AMD) is the leading cause of severe and irreversible vision loss among patients over 50 years of age [1,2]. Retinal pigment epithelial detachment (PED) occurs in association with AMD, often leading to decreased central vision due to retinal pigment epithelial (RPE) atrophy and also RPE tear [3]. Angiogenic factors such as vascular endothelial growth factor (VEGF) have been implicated in the development of choroidal neovascularization and have become the major targets in neovascular AMD therapy [4-7]. Currently, bevacizumab and ranibizumab (antiVEGF antibody) are the mainstay of treatment for neovascular AMD. Pivotal clinical trials such as MARINA [6] and ANCHOR [8], as well as PrONTO [9] have all demonstrated the efficacy of ranibizumab in terms of preservation and improvement of visual acuity in patients with neovascular ARM secondary to photodynamic therapy (PDT).

These studies have shown that about one third of patients with ARM improve in visual acuity by at least 15 letters [6,8], anecdotally we noted that a subset of these patients with pigment epithelial detachment (PED) more often than not, respond poorly to ranibizumab monotherapy. The goal of this study is to report our findings of ranibizumab monotherapy using variable dosing in these patients.

Materials and Methods

This is a retrospective, noncomparative chart review of patients who have neovascular AMD with pigment epithelial detachment. Institutional Review Board approval was obtained from Boston University Medical Center prior to initiation of the study. The charts of patients receiving ranibizumab monotherapy for neovascular AMD at the Boston University Eye Associates Retina clinic from July 1st 2006 to March 31st 2011 were retrospectively reviewed.

The inclusion criteria were patients at least 50 years age; had a Snellen visual acuity (VA) of at least 20/400; choroidal neovascularization secondary to age related macular degeneration with pigment epithelial detachment; treated with ranibizumab and the presence of at least one year of follow up data. Exclusion criteria were choroidal neovascularization due to other etiologies such as myopia, presumed ocular histoplasmosis, trauma and concurrent eye disease that may compromise visual acuity such as diabetic retinopathy and advanced glaucoma and previous treatment with subfoveal laser photocoagulation, Photodynamic Therapy (PDT) or pegaptanib (Macugen).

All eyes had been treated with intravitreal injections of ranibizumab 0.5mg. Injections were administered at baseline, month 1 and 2 and then on an as-needed basis at the discretion of the treating physician according to a 4 week clinical evaluation and OCT monitoring using the Stratus and Cirrus OCT (Carl Zeiss Meditec, Inc., Dublin, CA). Treatment was administered if there was evidence of any of the following signs: intraretinal fluid, subretinal fluid, worsening pigment epithelial detachment or retinal hemorrhage. Charts were reviewed for baseline demographic data, coexisting diagnoses, number of injections, VA at baseline as well as subsequent visits. Snellen VA was converted to logMAR.

*Corresponding author: Deeba Husain MD, Department of Ophthalmology, Boston University Medical Center, Contact Info: 85 East Concord Street, 8th floor, Boston MA 02118, USA, Tel: 617-414-2020; E-mail: deeba.husain@bmc.org

Received February 02, 2011; Accepted December 15, 2011; Published December 19, 2011

Citation: Akinwale A, Fenberg M, Vasquez V, Husain D (2011) Ranibizumab Monotherapy in Neovascular Age-Related Macular Degeneration with Pigment Epithelial Detachment. J Clinic Experiment Ophthalmol 2:129. doi:10.4172/2155-9570.1000199

Copyright: © 2011 Akinwale A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
to the logarithm of the minimal angle of resolution (logMAR) scale for statistical analyses [10]. Fluorescein angiograms were evaluated by a single retinal specialist (DH). All statistical analyses were performed on the Statistical Analyses System 9.1 system (SAS Inc., Cary, NC).

**Results**

A total of 85 patient charts were reviewed; 14 eyes of 12 patients were included in the study. Demographic characteristics of the patients are summarized in (Table 1).

Baseline fluorescein angiogram showed characteristics of neovascular AMD including the presence of PED. All PEDs were serous with evidence of choroidal neovascularization except one which had a hemorrhagic component. Other clinical findings including visual acuity and central macular thickness readings (CMT) are presented in (Table 2).

As shown in (Table 2), there was a decline in average visual acuity over the study period where the mean initial logMar was 0.596 (Snellen ~20/80) and mean final logMar was 1.018 (Snellen ~20/200). However, this decline in visual acuity was not statistically significant (p=0.05) despite treatment with ranibizumab. There was also no statistical significance between the mean initial and final CMT values, also indicating no overall improvement with treatment. The mean CMT increased by 19 microns over the duration of the study. (Figures 1 and 2) represent visual acuity and central macular thickness readings of each eye included in the study respectively. There were no significant complications including inflammation, retinal pigment epithelium tears or endophthalmitis associated with intravitreal ranibizumab injection administration.

To illustrate one of the responses to ranibizumab monotherapy, a case has been described below. A 63 year old female with complaint of acute decreased vision in her right eye, over 2 weeks. She was diagnosed with neovascular AMD with serous PED, given three consecutive monthly ranibizumab injections and subsequently followed monthly with administration of ranibizumab as needed. The PED appeared to resolve periodically only to re-accumulate during a period when no treatment was administered. Figures 3 and 4 show changes on OCT associated with administration of ranibizumab.

**Discussion**

The findings of this study indicate that ranibizumab monotherapy administered on an as needed basis is of questionable benefit in eyes with AMD and associated serous PED. This is consistent with the findings demonstrated by Ritter et al. [11] in a small prospective study which showed a decreased volume in the PED initially with ranibizumab.
monotherapy, however was ineffective in improving visual acuity over one year. The case presented illustrates a response to ranibizumab albeit not a permanent one. There were eyes that had minimal to no response to the injections with worsening of VA and CMT such as in eye #7 (Figures 1 and 2). There are a few theories surrounding the etiology of this particular group of patients that respond poorly to ranibizumab therapy. Limited response to ranibizumab could be attributed to the “wait and observe approach” or as-needed treatment in this study as opposed to the monthly regimen which was utilized in the MARINA and ANCHOR trials. We can also hypothesize that perhaps this is a different lesion such as retinal angiomatous proliferation [12, 13], which may require a different mode of therapy or more aggressive therapy such as triple therapy with PDT, intravitreal anti-VEGF therapy and intravitreal steroids [14]. The Verteporfin In Photodynamic Therapy Study (VIP) trial demonstrated that patients with AMD lost less lines of vision when treated with PDT [15], however Axer-Siegel et al. [16] found those patients with serous PED may not benefit at all from PDT. More recent studies have reported success in decreasing the number of required anti-VEGF injections and stabilizing vision with a combination of antiVEGF and PDT including for patients with PED [17, 18]. There are currently clinical trials in the pipeline investigating a combination of antiVEGF and PDT including for patients with PED number of required anti-VEGF injections and stabilizing vision with those patients with serous PED may not benefit at all from PDT. More recent studies have reported success in decreasing the number of required anti-VEGF injections and stabilizing vision with a combination of antiVEGF and PDT including for patients with PED [17, 18]. There are currently clinical trials in the pipeline investigating a combination of antiVEGF and PDT including for patients with PED. Limited response to ranibizumab alone when administered on an as-needed basis is not effective for the treatment of neovascular AMD with PED. The typical trend in neovascular AMD towards improved vision as well as a decrease in central macular thickness with anti-VEGF therapy was not noted in this study when compared to results from previous studies such as PRONTO, MARINA and ANCHOR. In the future, a prospective study which includes a large sample size would be able to provide additional useful information regarding the management of this subset of patients.

There are a few limitations of this study; it is a pilot study with a small sample size and it is retrospective in nature which contributes to selection bias. Though the limitations, this study suggests that ranibizumab alone when administered on an as-needed basis is not effective for the treatment of neovascular AMD with PED. The typical trend in neovascular AMD towards improved vision as well as a decrease in central macular thickness with anti-VEGF therapy was not noted in this study when compared to results from previous studies such as PRONTO, MARINA and ANCHOR. In the future, a prospective study which includes a large sample size would be able to provide additional useful information regarding the management of this subset of patients.

References

1. Klaver CC, Assink JJ, van Leeuwen R, Wolfs RC, Vingerling JR, et al. (2001) Incidence and progression rates of age-related maculopathy: the Rotterdam study. Invest Ophthalmol Vis Sci 42: 2237-2241.
2. Klein R, Wang Q, Klein BE, Moss SE, Meuer SM (1995). The relationship of age-related maculopathy, cataract, and glaucoma to visual acuity. Invest Ophthalmol Vis Sci 36: 182-191.
3. Deckers WL, Sanborn GE, Ridley M, Annesley WH, Serr OM (1983) Retinal pigment epithelial tears. Ophthalmology 90: 507-512.
4. Campa C, Costagliola C, Incovia C, Sheridan C, Semeraro F, et al. (2010) Inflammatory mediators and angiogenic factors in choroidal neovascularization: pathogenetic interactions and therapeutic implications. Mediators Inflamm 2010 pii: s46826.
5. Stone EM (2006) A very effective treatment for neovascular macular degeneration. N Engl J Med 355: 1493-1495.
6. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, et al. (2006) Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 355: 1419-1431.
7. Dadakostar H, Waheed N (2008). The evolving role of vascular endothelial growth factor inhibitors in the treatment of neovascular age-related macular degeneration. Eye (Lond) 22: 761-767.
8. Brown DM, Kaiser PK, Michels M, Soubrae G, Heier JS et al. (2006). Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 355: 1432-1444.
9. Fung AE, Laiwani GA, Rosenfeld PJ, Dubovy SR, Michels S, et al. (2007). An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol 143: 566-583.
10. Holladay JT (1997) Proper method for calculating average visual acuity. J Refract Surg 13: 388-391.
11. Ritter M, Bolz M, Sacu S, Deak GG, Kiss C et al. (2010). Effect of intravitreal ranibizumab in avascular pigment epithelial detachment. Eye (Lond) 24: 962-968.
12. Yannuzzi LA (2003) Retinal angiomatous proliferation in AMD. Rev Ophth 10:07.
13. Yannuzzi LA, Negrao S, Lida T, Carvalho C, Rodriguez-Coleman H, et al. (2001) Retinal angiomatous proliferation in age-related macular degeneration. Retina 21: 416-434.
14. Augustin AJ, Puls S, Offerman I (2007) Triple therapy for choroidal neovascularization due to age-related macular degeneration: verteporfin PDT, bevacizumab and dexamethasone. Retina 27: 133-140.

15. Verteporfin In Photodynamic Therapy Study Group (2001) Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of randomized clinical trial including lesions with occult and no classic choroidal neovascularization--verteporfin in photodynamic therapy report 2. Am J Ophthalmol 131: 541-560.

16. Axer-siegel R, Ehrlich R, Rosenblatt I, Kramer M, Priel E, et al. (2004) Photodynamic therapy for occult choroidal neovascularization with pigment epithelium detachment in age-related macular degeneration. Arch Ophthalmol 122: 453-459.

17. Shima C, Gomi F, Sawa M, Sakaguchi H, Tsujikawa M, et al. (2009) One-year results of combined photodynamic therapy and intravitreal bevacizumab injection for retinal pigment epithelial detachment secondary to age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 247: 899-906.

18. Mataix J, Palacios E, Carmen DM, Garcia-Pous M, Navea A, et al. (2010) Combined ranibizumab and photodynamic therapy to treat exudative age-related macular degeneration: an option for improving treatment efficiency. Retina 30:1190-1196.

19. University of California, Davis; Genentech. Retinal and Retinal Pigment Epithelium Autoimmunity in Age-related Macular Degeneration (AMD) - Correlation with Lucentis (R) Therapy (Antibody) In: ClinicalTrials.gov [internet]. National Library of Medicine (US). [cited 2010, Nov]. Available from http://clinicaltrials.gov/ct2/show/NCT00931489.

20. http://clinicaltrials.gov/ct2/show/NCT01189019

21. Schmidt-Erfurth U, Eldem B, Guymer R, Korobelnick J, Sclingemann RO, et al. (2010) Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. Ophthalmology 118: 831-839.

22. Regeneron Pharmaceuticals; Bayer. Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration AMD (VIEW1). In: ClinicalTrials.gov [internet]. National Library of Medicine (US). [cited 2011, Nov]. Available from http://clinicaltrials.gov/ct2/show/NCT00509795.