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Case Report Open Access

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

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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 258 to final CMT 277.08. There was no statistically significant difference between the initial and final CMT (p=0.60). 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 ARMD over photodynamic therapy (PDT).

These studies have shown that about one third of patients with ARMD 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

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to the logarithm of the minimal angle of resolution (logMAR) scale for statistical analyses [10]. Flourescein 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 choriodal 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 montotherapy, 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

Number of eyes	14
Mean age (range) years	77 (59-93)
Gender	
Male Female	14% 86%
Race	100% Caucasian

Table 1: Demographic characteristics of the study patients.

Mean visual acuity (LogMar) Initial Final	 0.5960 1.018
Mean follow up time (range) months	35 (17-62)
Mean number of injections (range)	10 (3-23)
Mean CMT (microns) Initial Final	 258.0 277.714

Table 2: Clinical data obtained including mean visual acuity, CMT and follow up time.

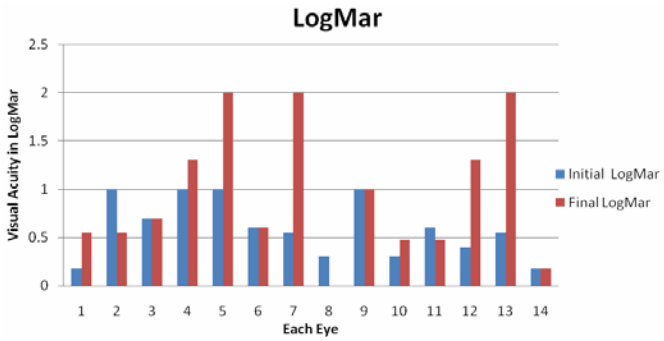

Figure 1: Mean LogMar visual acuity for each eye. Eye #8 had a snellen VA 20/20 which corresponds to LogMar zero, hence there is no bar.

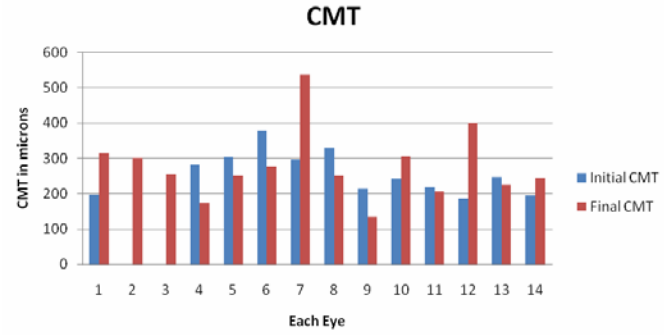

Figure 2: Mean central macular thickness for each eyes. Eyes #2 and #3 had no baseline OCT obtained.

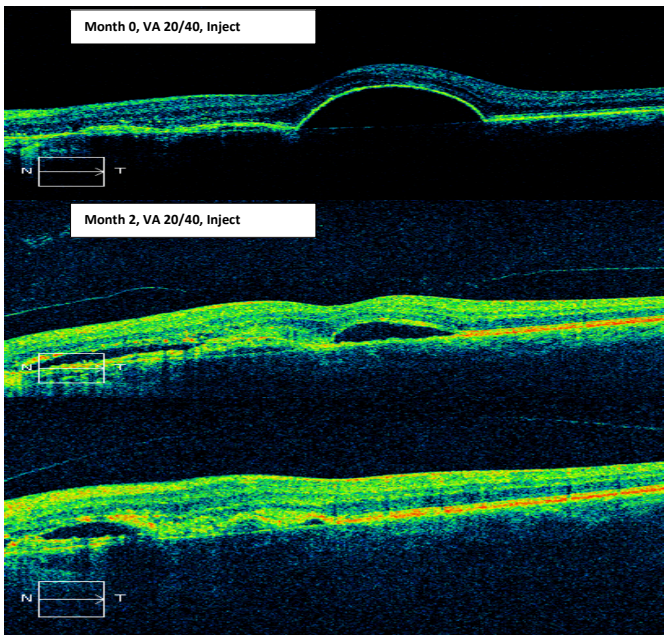

Figure 3: OCT response to ranibizumab injections from month 0 to month 2.

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

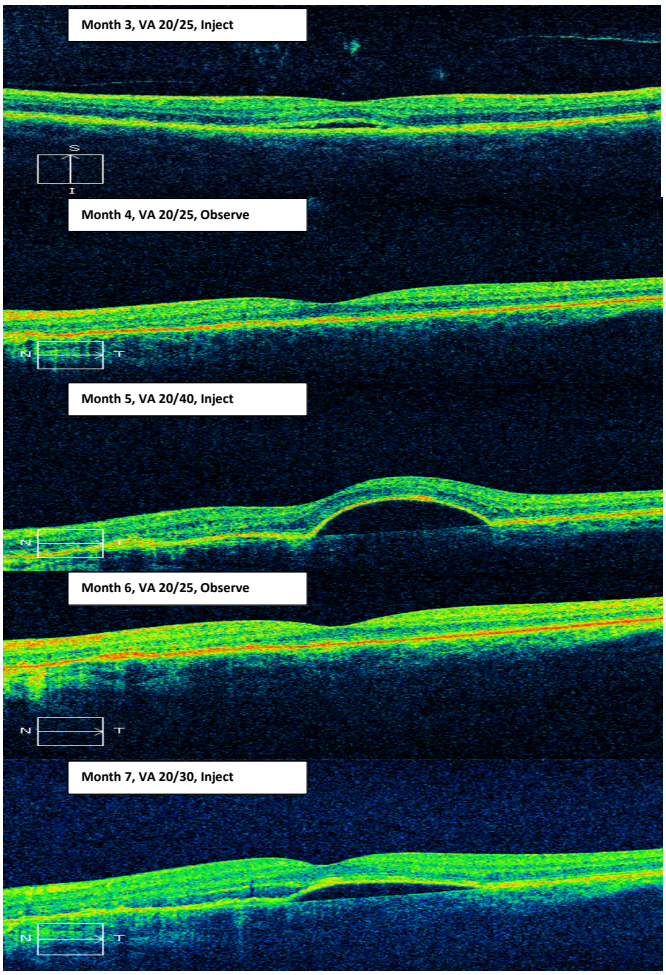

Figure 4: OCT response to ranibizumab injections from month 3 to month 10.

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 some theories that could result in management of this subset of patients. One such theory, reports that there is an abnormal autoimmunity activity in the RPE of these patients [19], while another observes the response of persistent PED lesions to high dose ranibizumab [20]. Results from the EXCITE study[21] comparing efficacy of monthly to quarterly ranibizumab treatment suggest that monthly treatments may result in better outcomes for patients with neovascular AMD - could this potentially translate to improvement for patients with PED. Most recently, aflibercept (VEGF Trap) which targets both VEGF-A and Placental Growth Factor (PIGF) has been found to be as effective as ranibizumab [22]; there is a possibility that this new regimen may be more effective in the minimally responsive subset of patients. This remains to be seen as further studies are performed.

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.

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