The Frequency of the Nonresponsiveness to Intravitreal Injection of the Anti-Vascular Endothelial Growth Factor Agent in Neovascular Age Related Macular Degeneration

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Abstract

Purpose: To investigate the frequency of nonresponsiveness to intravitreal injection of anti-vascular endothelial growth factor (VEGF) in treatment of neovascular age related macular degeneration (AMD)

Methods: A hundred eighty eyes of a hundred patients having inclusion criteria were reviewed. The medical records were evaluated retrospectively. Before one month and four months after intravitreal anti-VEGF injections, best corrected visual acuity (BCVA) to logMAR, fundus photography, optical coherence tomography (OCT) and fluorescein angiography (FA) findings were reviewed. Loss or no change in BCVA with persistent macular blood, intraretinal or subretinal fluid on OCT scans and leakage in FA despite continuing monthly anti-VEGF therapy were defined as nonresponsiveness. The numbers of nonresponder patients were calculated and the causes of nonresponsiveness were investigated. Fifty eight eyes of 33 patients with subfoveal choroidal neovascular membranes (CNVM) treating with the least three loading injection of one of anti-VEGF agents including pegaptanib, bevacizumab and ranibizumab for neovascular AMD were included the study.

Results: The 58 eyes (32%) of 180 eyes that received anti VEGF therapy were identified as nonresponders. Separately proportions of responsiveness to pegaptanib, bevacizumab and ranibizumab are %32, %17 and %51 respectively. Non responsiveness was seen in eyes administered pegaptanib (18 eyes)-bevacizumab (10 eyes) and ranibizumab (30 eyes). The ages of the patients were between 52 and 80, while the age averages were 64.6 years. Thirteen (39%) of the patients were female and 20 (61%) of them were male. Pretreatment and posttreatment mean BCVA to LogMAR units were 0.8 ± 0.16 and 1.5 ± 0.24 respectively (p<0.05). The mean injection number was five. The mean follow-up duration was 24 months. The nonresponders have showed dye leakage in FA and intraretinal/subretinal liquid in OCT and/or hemorrhage in ophthalmoscopy. Ten patients had systemic hypertension, and eight patients had diabetes mellitus. OCT revealed foveal scar in 6 eyes (10.3 %), serous retina pigment epithelium detachment (PED) in 14 eyes (24.1 %), fibrovascular PED in 17 eyes (29.3 %), hemorrhagic PED in 4 eyes (6.8%), vitreomacular traction syndrome (VMTS) in 10 eyes (17.2%), outer retinal edema in 2 eyes (3.4%) and foveal cystoid degeneration in 5 eyes (8.6%).

In the nonresponder patients to single anti-VEGF intervention, firstly, drug was switched to another one. All of the nonresponder patients to the switched drug interventions eventually underwent combination therapy including Photodynamic treatment (PDT) and intravitreal anti-VEGF drug injection such as ranibizumab or bevacizumab.

Conclusions: This study shows that the incidence for nonresponsiveness to single anti VEGF therapy in neovascular AMD is 32%. Some pathologies including foveal scarring, serous PED, fibrovascular PED, hemorrhagic PED and VMTS may be play a partly role in the nonresponsiveness to anti-VEGF agents. The fact that the prediction and description of the nonresponder cases to intravitreal anti-VEGF drugs in the treatment of neovascular AMD might prevent unnecessary treatment interventions.

Keywords

Neovascular age related macular degeneration; Anti vascular endothelial growth factor; Nonresponsiveness; Nonresponders; Frequency

Introduction

Age-related macular degeneration (AMD) is a major cause of irreversible visual loss in developed countries in 65 years and older [1-3]. The two types of AMD are non-neovascular type and neovascular type. Neovascular AMD is characterized by choroidal neovascular membrane (CNVM) that is due to the formation of abnormal blood vessels, which grow from the choroid into or under the retina [1]. Although CNVM is present in only 10% of patients with AMD, it is responsible for 90% of cases with severe vision loss from hemorrhage and fibrosis. The pathogenesis of CNVM is a complex process involving the disturbance between proangiogenic and antiangiogenic factors. The vascular endothelial growth factor (VEGF) that released by retina pigment epithelium cells (RPE) is the most important of the angiogenic factors to stimulate the growth of new vessels [3]. The formation of CNVM in AMD has been shown to be related to increase levels of VEGF. Anti-VEGF agents have dramatically improved the prognosis of patients with neovascular AMD [4,5].

Anti-VEGF agents are considered as the most hopeful way of effectively inhibition of the neovascular AMD process. Currently, 3 anti-VEGF agents are in clinical use; ranibizumab, pegaptanib and bevacizumab. Pegaptanib that first approved for the treatment of AMD is not a pan-anti-VEGF inhibitor. Recent studies have demonstrated that ranibizumab and bevacizumab which are known as pan anti-VEGF agents have beneficial morphological and functional outcomes in patients with CNVM secondary to AMD. The proportion of patients which visual acuity improved is in a range between 28%-43% [6-11]. However, some patients receiving intravitreal injections of these agents can not respond to the treatment as expected. Poor
responders to anti-VEGF agents are usually categorized into four groups: mistaken diagnosed patients, non responders, patients having tachyphylaxis and complication group [12-16]. Eyes which are initially diagnosed as AMD but later identified to have AMD variants like polypoidal choroidal vasculopathy (PCV), central serous chorioretinopathy (CSC) and retinal angiomatous proliferation (RAP) on the basis of indocyanine green angiography (ICGA) are entered the “mistaken diagnosis” group. Eyes that showed good response to anti VEGF therapy in the form of resolution of the fluid after the loading dose and developing recurrence of fluid with the increase inspite of additional anti VEGF therapy were classified under “tachyphylaxis”. Eyes with good response to anti VEGF therapy but with complications like RPE tear, macular scarring, and endophthalmitis that cause to decrease in vision form the “complications” group [12-16].

An anti-VEGF nonresponder is described as a patient which has loss or no change in either visual acuity or/and reading ability despite continuing monthly anti-VEGF therapy with persistent macular blood, intraretinal or subretinal fluid on optical coherence tomography (OCT) scans and leakage in florescein angiography (FA) [12-16].

The aim of this study is to investigate the frequency of nonresponsiveness to intravitreal injection of anti-VEGF in treatment of neovascular AMD.

Materials and Methods

This retrospective study involved eyes that were diagnosed as having neovascular AMD and treated with anti VEGF therapy at Firat University Hospital.

The diagnosis of neovascular AMD was made on the basis of clinical examination with indirect ophthalmoscopy and FA. Fifty eight eyes of 33 patients with subfoveal CNVM treating with the least three loading injections of one of anti-VEGF agents including pegaptanib, bevacizumab and ranibizumab for neovascular AMD were included in the study. The medical records were evaluated retrospectively. Before one month and four month after intravitreal anti-VEGF injections, best corrected visual acuity (BCVA) to logMAR, fundus photography, OCT and FA findings were reviewed. Loss or no change in BVCA with persistent macular blood, intraretinal or subretinal fluid on OCT scans and leakage in FA despite continuing monthly anti-VEGF therapy were defined as nonresponsiveness. All eyes were treated with a protocol including 3 consecutive monthly injections of antiVEGF agent similar to that in the PRONTO study. Following the loading doses these patients were followed up at monthly intervals for one year. Presence of activity was primarily studied on the OCT and FA performed whenever necessary. OCT (Spectral OCT/SLO OTI/OPKO, Toronto, Canada) was used to detect macular edema, subretinal fluid accumulation and pigment epithelium detachment (PED). OCT criteria for retreatment was based on the PRONTO study [17]. Indocyanine green angiography was done when treating ophthalmologist considered to be required. Only nonresponder eyes to anti VEGF therapy were included in this study. The eyes with mistaken diagnosis, tachyphylaxis, and complication were excluded from the study. The numbers of nonresponder patients were calculated and the causes of nonresponsiveness were investigated.

In the treatment of the patients having evidence of nonresponse, alternate bevacizumab or ranibizumab injection was used. In the other words, drugs were switched from one drug to another for the treatments of these patients. Despite to the drug switching, the patients which can not response to monotherapy were performed combination therapy (photodynamic therapy with Verteporfin and anti-VEGF agent). The study was conducted according to Helsinki Declaration. The study was designed as an institutional, retrospective trial. Informed consents were obtained from the patients. Additionally, informed consents were taken for off label use of bevacizumab from all patients whenever used.

The pars plana injection technique

Before the injection is administered, oxybuprocaine hydrochloride drop and 10% povidone-iodine wash using a flush injector were applied directly to the ocular surface, lid margins, and lashes. After a lid speculum was placed, an additional drop of povidone-iodine and topical anaesthetic was applied to the intended injection site. No instrument was performed for the globe fixation during the injection because the potential elevation of intraocular pressure due to fixation might influence reflux. Injection of 0.5 mg/0.05 mL ranibizumab (Lucentis; Genentech Inc., South San Francisco, CA) or 2.5 mg/0.1 mL bevacizumab or 0.3 mg/0.1 mL pegaptanib (Macugen; Eyetech Pharmaceuticals, New York, USA) was performed through the pars plana using a 27 gauge needle on a tuberculin syringe (bevacizumab) or 30 gauge needle on own syringe for drug (ranibizumab) in temporal quadrants 3 mm (pseudophakic eyes) to 4 mm (phakic eyes) from the limbus.

The standard straight injection perpendicular to the sclera was slowly created after upward mobilization of the conjunctiva and the syringe needle was then gently withdrawn. In order to avoid vitreous wick syndrome, the conjunctiva shifted with a cotton-tipped applicator before injection and then, to minimize reflux, this applicator was softly applied over the scleral entry site to the needle withdrawn for about three seconds. Before the after injection, retinal artery perfusion was checked by indirect ophthalmoscopy. One drop of 3% ofloxacin was prescribed four times a day for 5 days. Following the injection, the patients were warned to refer the clinic in case of unexpected conditions and to have to come follow-up visits at day 1 and day 5 to check for possible complications.

Results

Out of the 180 eyes that received anti VEGF therapy 58 eyes (32%) that did not show complete resolution of fluid at any point of time during follow up were identified as non responders. Separately proportions of responsiveness to pegaptanib, bevacizumab and ranibizumab are %32, %17 and %51 respectively. Non responsiveness was seen in eyes administered pegaptanib (18 eyes), bevacizumab (10 eyes) and ranibizumab (30 eyes) (Table 1). All the patients were primarily diagnosed to have subfoveal CNVM on FA. The ages of the patients were between 52 and 80, while the age averages were 64.6 years. Thirteen (39%) of the patients were female and 20 (61%) of them were male. Pretreatment and posttreatment mean BCVA were 0.8 ± 0.16 LogMAR and 1.5 ± 0.24, respectively (p<0.05). The mean

Table 1: Numbers and percentages of nonresponder patients in subgroups.

<table>
<thead>
<tr>
<th>Nonresponsiveness Subgroups</th>
<th>Eyes (%)</th>
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<tbody>
<tr>
<td>Pegaptanib group</td>
<td>18 (%32)</td>
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<tr>
<td>Bevacizumab group</td>
<td>10 (%17)</td>
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<tr>
<td>Ranibizumab group</td>
<td>30 (%51)</td>
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injection number received per person over one year of follow up was five. The mean follow-up duration was 24 months. The nonresponders have showed dye leakage in FA and intraretinal/subretinal liquid in OCT and hemorrhage in ophthalmoscopy. Ten patients had systemic hypertension, and eight patients had diabetes mellitus. Baseline OCT scans revealed foveal scar in 6 eyes (10.3 %), serous retina pigment epithelium detachment (PED) in 14 eyes (24,1%), fibrovascular PED in 17 eyes (29,3%), hemorrhagic PED in 4 eyes (6,8%), cystoid foveal degeneration in 5 eyes (8,6%), vitreomacular traction syndrome (VMTS) in 10 eyes (17,2%) and outer retinal tubulation in 2 eyes (3,4%) (Table 2).

Of 58 nonresponders eyes, 18 eyes primarily received pegaptanib, 10 eyes received primarily bevacizumab, 30 eyes received primarily ranibizumab. In 5 eyes that received ranibizumab, drug switched to bevacizumab and in 5 eyes that received bevacizumab, drug switched to ranibizumab during follow up. The eyes applied alternate drug injections were remained as nonresponders, again.

All of the nonresponder patients to the switched drug interventions eventually underwent combination therapy including Photodynamic treatment (PDT) and intravitreal anti-VEGF drug injection such as ranibizumab or bevacizumab.

Any complication requiring treatment such as endophthalmitis, increased intraocular pressure, retinal tear and retinal detachment was not occurred during the follow up period. The mean interval between consecutively injections was 4 weeks. Forty of nonresponders eyes had the classic type CNVM and 18 of them had occult CNVM.

Discussion

Recent clinical trials on ranibizumab and bevacizumab in neovascular AMD demonstrated the capability of these drugs to improve mean visual acuity over the course of two years when administered intravitreally on a monthly basis. According to MARINA and ANCHOR studies, it is well known that ten percent of patients with neovascular AMD can lose a significant amount of vision despite two years of the treatment with monthly anti-VEGF injection [10,17-19]. Although there is no definitive management of the failure in anti-VEGF treatment, in the management for the nonresponsiveness to anti-VEGF agents, continued anti-VEGF blockade alternating bevacizumab and ranibizumab every two weeks, or combination therapy including anti-VEGF blockade and/or PDT and/or intravitreal corticosteroids can be used [12-17].

The response proportion for both ranibizumab and bevacizumab are approximately 95%. To predict the failure of anti-VEGF treatment is difficult, however one study demonstrated that the efficacy of anti-VEGF therapy was depended on the initial lesion size and initial reading ability. With a bigger CNVM size and a lower reading ability, the chance of responding appears to be reduced [14].

An anti-VEGF nonresponder is described a patient which has loss or no change in either visual acuity or/and reading ability despite continuing monthly anti-VEGF therapy with persistent macular blood, intraretinal or subretinal fluid on OCT scans and leakage in FA [12-16].

In a study on anti-VEGF nonresponsiveness, Lux et al reported that the 45% of the patients were non-responders to bevacizumab. In their study, it was also reported that the possibility of nonresponsiveness to bevacizumab might be depend on initial lesion size, but was independent of the amount of intraretinal and subretinal fluid [14].

In recent two studies belong to Ladewig et al. and Rich et al. [20,21], the proportion of non-responders to bevacizumab seem as approximately 50%. In our study, the proportions of nonresponders to all of antiVEGF drugs are 32%. Separately proportions of responsiveness to pegaptanib, bevacizumab and ranibizumab are %32, %17 and %51 respectively. These percents are in consistent with recent studies.

In our study, baseline OCT scans of nonresponder patients revealed some pathologies including foveal scarring, serous PED, fibrovascular PED, hemorrhagic PED and VMTS. So, these may be play a partly role in the nonresponsiveness to anti-VEGF agents. Nonresponsiveness may result from a number of factors including the development of subfoveal fibrosis or atrophy of the RPE and photoreceptors. In recent studies, it has been emphasized that the efficiency of antiVEGF agents might be reduced because of a large initial CNVM having a greater fibrosis or lesser viable RPE [14,22] or underlying genetic differences [23,24] or an anti-VEGF resistance.

Conclusions

The prediction of which patient will respond to an anti-VEGF agent is not easy. Neovascular AMD patients having foveal scarring, serous PED, fibrovascular PED, hemorrhagic PED and VMTS might be at the risk for nonresponsiveness to these agents. So, anti-VEGF interventions for these patients should be use selectively. To prediction and to description individuals who might be considered as nonresponders to anti-VEGF drugs using in the treatment of neovascular AMD might prevent unnecessary treatment interventions, consequently it might reduce treatment costs and unrealistic patient expectations. Large randomised clinical trials with long-term follow-up are needed to define reasons of nonresponsiveness to anti-VEGF injections in the treatment of neovascular AMD.

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Involved in the conduct of study (BT and RT); collection of data, typing and editing of manuscript; statistical analysis and editing of manuscript (BT and RT) and preparation, review, or approval of the final manuscript (BT and RT).

References


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