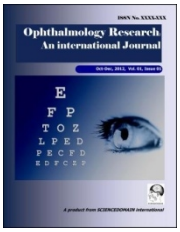

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Tachyphylaxis to ranibizumab in the Treatment of Age-related Macular Degeneration

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Authors' contributions

This work was carried out in collaboration between all authors. Author TO designed the study, wrote the protocol and helped write the first draft of the manuscript. NKmanaged the literature searches, analyzedthe data and wrote the first draft. Authors TO, NK and AT saw patients in this research. Authors TN and KT oversaw all aspects of the study. All authors read and approvedthe final manuscript.

Original Research Article

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ABSTRACT

Purpose: To assess the patients with exudative age-related macular degeneration (AMD) who develop tachyphylaxis to ranibizumab after intravitreal injections of ranibizumab (IVR).
Methods: We reviewed the records of 115 eyes of 110patients who received IVR from April 2009 to September 2011 at the Kansai Medical University, Takii Hospital. Among the patients who were not regarded as initial non-responders, patients whose response deteriorated after repeated intravitreal use of ranibizumab were defined as having tachyphylaxis.
Results: In this study, we found a 5.2% rate (6/115) of subjects with tachyphylaxis. Two eyes of those with tachyphylaxis had a classic choroidal neovascularization component. There was no significant difference in lesion types between patients with tachyphylaxis and responders (P=0.47; chi-square test).
Conclusion: There are a few percentages of AMD patients who develop tachyphylaxis to ranibizumab. No significant difference is observed in the prevalence of tachyphylaxis among the lesion types.

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Keywords: Age-related macular degeneration; anti-vascular endothelial growth factor drug; choroidal neovascularization; ranibizumab; tachyphylaxis.

ABBREVIATIONS

OCT- Optical Coherence Tomography, AMD- Age-Related Macular Degeneration, CNV-Choroidal Neovascularization, SRF- Subretinal Fluid.

1. INTRODUCTION

Exudative age-related macular degeneration (AMD) is the majorcause of visual acuity loss among the older people [1]. The formation of choroidal neovascularization (CNV) damages the macular region, which results in severe vision impairment [2]. Intravitreal injection of anti-vascular endothelial growth factor drugs (anti-VEGF drugs) has become the established and widely recognized treatment for AMD.

Administration of ranibizumab is one of the majortreatments for exudative AMD. It not only prevents visual acuity loss, but also improves visual acuity [3]. The MARINA [3] and ANCHOR [4] studies have shown that ranibizumab was effective for patients with any type of AMD at the primary 12-month assessment. The efficacy has also been shown through the final 24-month assessment [5]. Moreover, the HORIZON studyhas shown the 3-year safety and efficacy of intravitreal injection of ranibizumab (IVR) [6].

Among the patients with AMD who receive a loading dose of three intravitreal ranibizumab injections, there are some patients who show no response to ranibizumab. Those patients are classified as initial non-responders. Among the patients who are not regarded as initial non-responders, there are some patients whose responses decrease after repeated administrations. These cases are said to have tachyphylaxis. In general, tachyphylaxis can developin a short period when drugs are administered repeatedly. No responses occur even though the dosage is increased. Efficacy can be restored if the drug holidays are taken. Tachyphylaxis has been reported in the setting of other biologic agents including β-interferon, infliximab and natalizumab [7-9]. In this report, we assessed a retrospective case series of patients who developed tachyphylaxis with AMD who were treated with IVR.

2. MATERIALS AND METHODS

We reviewed the records of 115 eyes of 110patients who received IVR from April 2009 to September 2011 at the Kansai Medical University, Takii Hospital. This retrospective study was performed with informed patient consent and was conducted in accordance with the principles of the Declaration of Helsinki. Patientsreceived three IVR treatments every 4 weeks for their initial treatment. After the treatments, they were retreated if visual acuity decreased or subretinal fluid was observed. The surgeon gave an intravitreal injection of ranibizumab (0.5 mg/0.05 ml) at 3.5mm posterior to the limbus in pseudophakic eyes and 4.0mm posterior to the limbus in phakiceyes. We followed up the patients for at least 12 months. Patients with polypoidal choroidal vasculopathy and retinal angiomatous proliferation were excluded. Patients with high myopia were also excluded. We excluded the cases that had photodynamic therapy (PDT) during the induction phase. Spectral domain optical coherence tomography (OCT) (RTVue-100 (Optovue Inc., Fremont, CA)) was used to measure the central retinal thickness (CRT). Patients were seen approximately every four weeks and a comprehensive ophthalmic examination including best-corrected visual acuity (BCVA) and OCT imaging was performed at every visit.

We defined patients whose BCVA do not improve and CRT do not decrease at the induction phase as initial non-responders to ranibizumab. We used the same definition of initial non-responders as that used in a previous report [10]. Among the patients who were not considered as initial non-responders, patients whose response deteriorated after at least six IVR within a year were defined as having tachyphylaxis. BCVA was measured with a Japanese standard decimal visual chart and the logarithm of the minimum angle of resolution (logMAR) scale was used for statistical analysis. A marked change in visual acuity was defined as a difference of 0.3 or more units of logMAR visual acuity. A marked change in CRT measured by OCT was defined as a difference of 10% or more. Chi-square test and unpaired t-test were used for statistical analysis.

3. RESULTS

A total of 110 patients (81 male, 29 female, mean age: 73.4 years) were included in this study. Sixty five eyes had occult CNV without classic component, 17 had minimally classic CNV and 33had predominantly classic CNV. Fifty eyes had a classic CNV component and 65 eyes did not have a classic CNV component.

Twelveof 115eyes (10.4%) were identified as initial non-responders, and 6 of 115 eyes (5.2%) were identified as having tachyphylaxis. We called the remaining patients responders (84.4%).

The logMAR visual acuity before the treatment was 0.55 in patients with tachyphylaxis, 0.39 in initial non-responders, and0.55 in responders. There was no significant difference in logMAR visual acuity between patients with tachyphylaxis and responders (P=0.97; unpaired t-test). The CRT before the treatment was 551 μm in patients with tachyphylaxis, 285 μm in initial non-responders, and 468 μm in responders. There was no significant difference in CRT between patients with tachyphylaxis and responders (P=0.32; unpaired t-test).Table 1 shows the characteristics of patients with tachyphylaxis, initial non-responders and responders in this study. The mean GLD before the treatment was 4585μm in eyes with tachyphylaxis, 4308μm in initial non-responders and 4205μm in responders. There was no significant difference between GLD in eyes with tachyphylaxis and that in responders (P=0.69; unpaired t-test).

Table 2 shows the lesion types in eyes with tachyphylaxis, initial non-responders and responders. Twoeyes of those with tachyphylaxis had a classic CNV component. Therewas no significant difference in lesion types between eyes with tachyphylaxis and responders (P=0.47; chi-square test).

Two eyes with tachyphylaxis received PDT and exudation was not found in these patients. One eye had three injections of pegaptanib (Fig. 1). This patient received IVR again after treatment with pegaptanib, and the macular exudation of the patient was resolved.

An 80-year-old man with typical AMD A. At baseline, an OCT image shows type 1 CNV and subretinal fluid (SRF) in the macular area. B. After 3 consecutive monthly intravitreal injections of ranibizumab, no SRF is seen in OCT. C. After 7 injections of ranibizumab, an OCT image shows recurrent SRF with 1.0 logMAR visual acuity. D. Therapy was switched to pegaptanib injections, and SRF was decreased and the BCVA improved to 0.7 logMAR visual acuity after 1 injection of pegaptanib. E. After 3 injections of pegaptanib, there was an increase in SRF with 0.8 logMAR visual acuity. F. Therapy was switched to ranibizumab injections again, and the SRF was resolved with 0.7 logMAR visual acuity following 1 ranibizumab injection.

Table 1. Characteristics of subjects with tachyphylaxis, initial non-responders, and responders

	No of eyes (%)	Mean age	Mean GLD(μm)
Subjects with tachyphylaxis	6 (5.2%)	74	4585
Initial non-responders	12 (10.4%)	67	4308
Responders	97	74	4205

*P=0.99 (unpaired t-test)

**P=0.69 (unpaired t-test)

Notes: The mean GLD before the treatment was 4585 μm in eyes with tachyphylaxis and 4205 μm in responders. There was no significant difference between them (P=0.69; unpaired t-test).

Abbreviations: GLD, greatest linear dimension

Table 2. Lesion types in subjects with tachyphylaxis, initial non-responders, and responders

	Classic component(-)	Classic component(+)
Subjects with tachyphylaxis	N=4	N=2
Initial non-responders	N=11	N=1
Responders	N=50	N=47

*P=0.008 (chi-square test for independence)

**P=0.47 (chi-square test for independence)

Notes: In patients with typical AMD, 2 eyes of those with tachyphylaxis had a classic CNV component. There was no significant difference in lesion types between eyes with tachyphylaxis and responders (P=0.47; chi-square test).

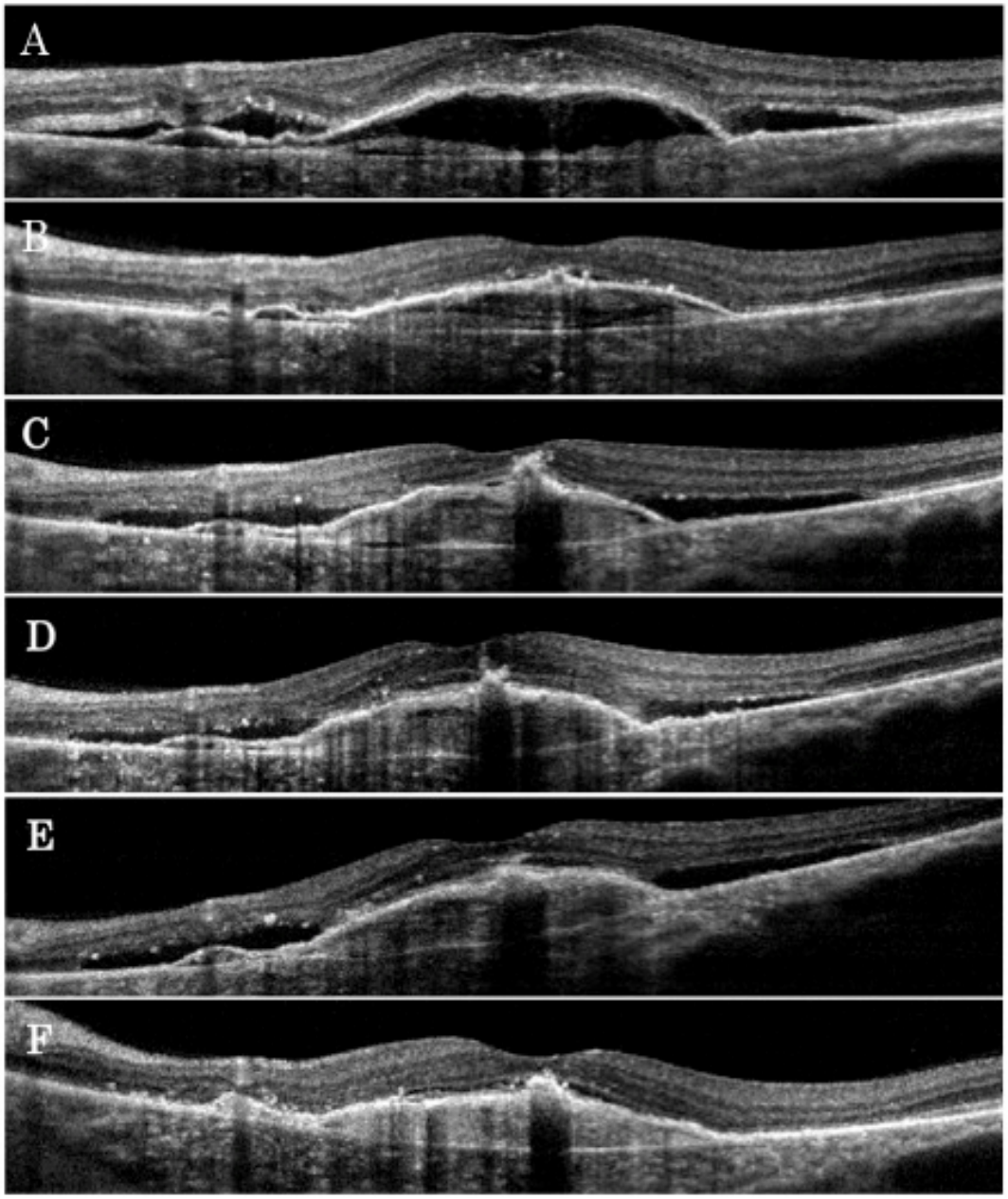

Fig. 1. Clinical course and OCT images for a patient with tachyphylaxis

4. DISCUSSION

In recent years, anti-VEGF drugs have been found to be effective for exudative AMD. These agents have been shown to prevent the deterioration of visual acuity or even improve visual acuity in AMD patients [3,11]. However, there are some patients who seem not to respond to the drug at all at the induction phase. We called those patients initial non-responders. We

reported previously that 10.1% of AMD patients were initial non-responders [10]. On the other hand, there were other patients whose response to the drug seemed to decrease gradually after repeated treatments. We defined those cases as patients who developed tachyphylaxis.

The reason why tachyphylaxis occurs has not been completely explained yet. However, there are possibly some factors that play a role in the development of tachyphylaxis. Tachyphylaxis may occur because of neutralization of ranibizumab [3]. Ranibizumab is a humanized monoclonal antibody. However, repeated injections might induce neutralizing antibodies. Another mechanism could be upregulation of the receptors [12]. Because of upregulation of the receptors, the amount of intravitreal ranibizumab may not be enough to shut down the process. Another explanation could be upregulation of the production of VEGF by macrophages [13]. Macrophages have been considered to induce the secretion of VEGF as well as retinal pigment epithelium cells. Another mechanism could be reactivation of the CNV driven by other pathways such as ICAM-1, E-selectin, CD44 and basic and acidic fibroblast growth factors [14]. A change in CNV is another possible cause for developing tachyphylaxis. Permanent structural damage to the vascular walls of the CNV could result in abnormal vascular permeability and persistent exudation [13]. To avoid a decrease in the effect of the drug because of tachyphylaxis, some possible solutions have been reported. Tachyphylaxis can be reduced using combination therapy and taking drug holidays. Less development of tachyphylaxis would be expected when using the PRONT protocol than the repeated use of drugs [12].

There have been some reports that have described tachyphylaxis to intravitreal anti-VEGF therapy. Keane et al. first reported possible tachyphylaxis in AMD following treatment with ranibizumab for CNV [15]. Schaal et al. suggested that combined therapy with triamcinolone acetate decreased the effect of tachyphylaxis to IVR for the treatment of exudative AMD [16]. Forroghian et al. [13] reported that 10.2% of the cases had tachyphylaxis after repeated intravitreal injections of bevacizumab. Gasperini et al. [17] reported that patients who developed tachyphylaxis to ranibizumab or bevacizumab might respond to another anti-VEGF drug. Eghøj et al. reported that 2% of AMD patients developed tachyphylaxis [12].

The mechanism for having no response seems to be unlike that for tachyphylaxis. It is considered that, in cases of initial non-responders, VEGF is not related to the pathophysiology of AMD because anti-VEGF drugs do not demonstrate an effect at the initial therapy. However, patients with tachyphylaxis to ranibizumab might respond to other anti-VEGF drugs. Intravitreal aflibercept has become an effective treatment for the patients with AMD [18]. Patients with tachyphylaxis to ranibizumab may show a desirable response using treatment regimen with aflibercept [19,20].

5. CONCLUSION

In conclusion, there are a few percentages of AMD patients who develop tachyphylaxis to ranibizumab. No significant difference is observed in the prevalence of tachyphylaxis among the lesion type of CNV. In future trials, the mechanisms of the development of tachyphylaxis need to be elucidated, and additional treatments to have ideal responses with anti- VEGF therapy need to be developed.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Bressler NM, Bressler SB, Congdon NG, Ferris FL 3rd, Friedman DS, Klein R, et al. Potential public health impact of Age-Related Eye Disease Study results: AREDS report no.11. Arch Ophthalmol. 2003;121(11):1621-4.
2. Klein R, Peto T, Bird A, Vannewkirk MR. The epidemiology of are-related macular degeneration. Am J Ophthalmol. 2004;137(3):486-95.
3. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. for MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1419-31.
4. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. for ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age- related macular degeneration. N Engl J Med. 2006;355(14):1432-44.
5. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T.for 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.
6. Singer MA, Awh CC, SaddaS,Freeman WR, Antoszyk AN, Wong P, et al. HORIZON: An open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. Ophthalmology. 2012;119(6):1175-83.
7. Fox EJ, Vartanian TK, Zamvil SS. The immunogenicity of disease-modifying therapies for multiple sclerosis: clinical implications for neurologists. Neurologist. 2007;13(6):355-362.
8. Calabresi PA, Giovannoni G, Confavreux C, Galetta SL, Havrdova E, Hutchinson M, et al. The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL. Neurology. 2007;69(14):1391-1403.
9. Svenson M, Geborek P, Saxne T, Bendtzen K. Monitoring patients treated with anti-TNF-alpha biopharmaceuticals: assessing serum infliximab and anti-infliximab antibodies. Rheumatology (Oxford). 2007;46(12):1828-1834.
10. Otsuji T, Nagai Y, Sho K, Tsumura A, Koike N, Tsuda M, et al. Initial non-responders to ranibizumab in the treatment of age-related macular degeneration (AMD). Clin Ophthalmol. 2013;7:1487-90.
11. Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology. 2006;113(3):363-72.e5.
12. Eghøj MS, Sørensen TL. Tachyphylaxis during treatment of exudative age-related macular degeneration with ranibizumab. Br J Ophthalmol. 2012;96(1):21-3.
13. Forooghian F, Cukras C, Meyerle CB, Chew EY, Wong WT. Tachyphylaxis after intravitreal bevacizumab for exudative age-related macular degeneration. Retina. 2009;29(6):723-31.

14. Shen WY, Yu MJ, Barry CJ, Constable IJ, Rakoczy PE. Expression of cell adhesion molecules and vascular endothelial growth factor in experimental choroidal neovascularization in the rat. Br J Ophthalmol. 1998;82(9):1063-71.
15. Keane PA, Liakopoulos S, Ongchin SC, Heussen FM, Msutta S, Chang KT, et al. Quantitative subanalysis of optical coherence tomography after treatment with ranibizumab for neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci. 2008;49(7):3115-20.
16. Schaal S, Kaplan JG, Tezel TH. Is there tachyphylaxis to intravitreal anti-vascular endothelial growth factor pharmacotherapy in age-related macular degeneration? Ophthalmology. 2008;115(12):2199-205.
17. Gasperini JL, Fawzi AA, Khondkaryan A, Lam L, Chong LP, Eliott D, et al. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation. Br J Ophthalmol. 2012;96(1):14-20.
18. Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012;119(12):2537-48.
19. Yonekawa Y, Andreoli C, Miller JB, Loewenstein JI, Sobrin L, Eliott D, et al. Conversion to Aflibercept for chronic refractory or recurrent neovascular age-related macular degeneration. Am J Ophthalmol. 2013;156(1):29-35.
20. Bakall B, Folk JC, Boldt HC, Sohn EH, Stone EM, Russell SR, et al. Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab. Am J Ophthalmol. 2013;156(1):15-22.

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