

Original Research Article**Tachyphylaxis to ranibizumab in the treatment of age-related macular degeneration****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 154 eyes of 152 patients 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 4.5% rate (7/154) of subjects with tachyphylaxis. In patients with typical AMD, 2 eyes of those with tachyphylaxis had a classic choroidal neovascularization (CNV) component. There was no significant difference in lesion types between patients with tachyphylaxis and responders ($P=0.47$; chi-square test). However, patients having tachyphylaxis had a lower prevalence of a classic CNV component than responders.

Conclusion: We found more patients with tachyphylaxis with occult CNV than patients with other types of lesions.

19 Key words: age-related macular degeneration, anti-vascular endothelial growth factor drug,
20 choroidal neovascularization, ranibizumab, tachyphylaxis

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22 **1. INTRODUCTION**

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

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

34 Among the patients with AMD who receive a loading dose of three intravitreal ranibizumab
35 injections, there are some patients who show no response to ranibizumab. Those patients are
36 classified as initial non-responders. Among the patients who are not regarded as initial

37 non-responders, there are some patients whose responses decrease after repeated
38 administrations. These cases are said to have tachyphylaxis. In general, tachyphylaxis can
39 develop in a short period when drugs are administered repeatedly. No responses occur even
40 though the dosage is increased. Efficacy can be restored if the drug holidays are taken.
41 Tachyphylaxis has been reported in the setting of other biologic agents including β -interferon,
42 infliximab and natalizumab [7-9]. In this report, we assessed a retrospective case series of
43 patients who developed tachyphylaxis with AMD who were treated with IVR.

44

45 **2. MATERIAL AND METHODS**

46 We reviewed the records of 154 eyes of 152 patients who received IVR from April 2009 to
47 September 2011 at the Kansai Medical University, Takii Hospital. This retrospective study was
48 performed with informed patient consent and was conducted in accordance with the principles of
49 the Declaration of Helsinki. A total of 152 patients (105 male, 47 female, mean age: 73.4 years)
50 were included. They received three IVR treatments every 4 weeks for their initial treatment. After
51 the treatments, they received IVR as needed. We followed up the patients for at least 12 months.
52 Patients with high myopia were excluded. We also excluded the cases that had photodynamic
53 therapy (PDT) during the induction phase. Spectral domain optical coherence tomography (OCT)
54 (RTVue-100 (Optovue Inc., Fremont, CA)) was used to measure the central retinal thickness

55 (CRT).

56 We defined patients whose BCVA do not improve and CRT do not decrease at the induction
57 phase as initial non-responders to ranibizumab. We used the same definition of initial
58 non-responders as that used in a previous report [10]. Among the patients who were not
59 considered as initial non-responders, patients whose response deteriorated after at least six IVR
60 within a year were defined as having tachyphylaxis. A marked change in visual acuity was
61 defined as a difference of 0.3 or more units. A marked change in CRT measured by OCT was
62 defined as a difference of 10% or more.

63

64 **3. RESULTS**

65 In this study, there were 115 eyes with typical AMD, 37 eyes with polypoidal choroidal
66 vasculopathy (PCV) and 2 eyes with retinal angiomatous proliferation (RAP). Among eyes with
67 typical AMD, 65 eyes had occult CNV, 17 eyes had minimally classic CNV and 33 eyes had
68 predominantly classic CNV. Fifty eyes had a classic CNV component and 65 eyes did not have a
69 classic CNV component. The mean greatest linear dimension (GLD) was 4239.7 μm .

70 Nineteen of 154 eyes (12.3%) were identified as initial non-responders, and 7 of 154 eyes (4.5%)
71 were identified as having tachyphylaxis. We called the remaining patients responders (83.2%).
72 Table 1 shows the characteristics of patients with tachyphylaxis, initial non-responders and

73 responders in this study. The mean GLD before the treatment was 3896 μm in eyes with
 74 tachyphylaxis, 4611 μm in initial non-responders and 4271 μm in responders. There was no
 75 significant difference between GLD in eyes with tachyphylaxis and that in responders ($P=0.51$;
 76 chi-square test).

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

	No of eyes (%)	Mean age	Mean GLD(μm)
Subjects with tachyphylaxis	7 (4.5%)	75	3896
Initial non-responders	19 (12.3%)	68	4611
Responders	128	74	4271

* $P=0.71$ (chi-square test for independence)

** $P=0.51$ (chi-square test for independence)

Notes: The mean GLD before the treatment was 3896 μm in eyes with
 tachyphylaxis and 4271 μm in responders. There was no significant difference between them
 ($P=0.51$; chi-square test).

Abbreviations: GLD, greatest linear dimension

77
 78
 79 Table 2 shows the subtypes of AMD in eyes with tachyphylaxis, initial non-responders and
 80 responders. In patients with tachyphylaxis, there were 6 eyes with typical AMD and 1 eye with
 81 PCV. There were no significant differences in the subtypes of AMD between eyes with
 82 tachyphylaxis and responders ($P=0.59$; chi-square test). Table 2 also shows the lesion types in

83 eyes with tachyphylaxis, initial non-responders and responders. In patients with typical AMD, 2
 84 eyes of those with tachyphylaxis had a classic CNV component. Patients having tachyphylaxis
 85 had a lower prevalence of a classic CNV component than responders. However, there was no
 86 significant difference in lesion types between eyes with tachyphylaxis and responders ($P=0.47$;
 87 chi-square test).

Table 2. Subtypes of AMD and lesion types in subjects with
 tachyphylaxis, initial non-responders, and responders

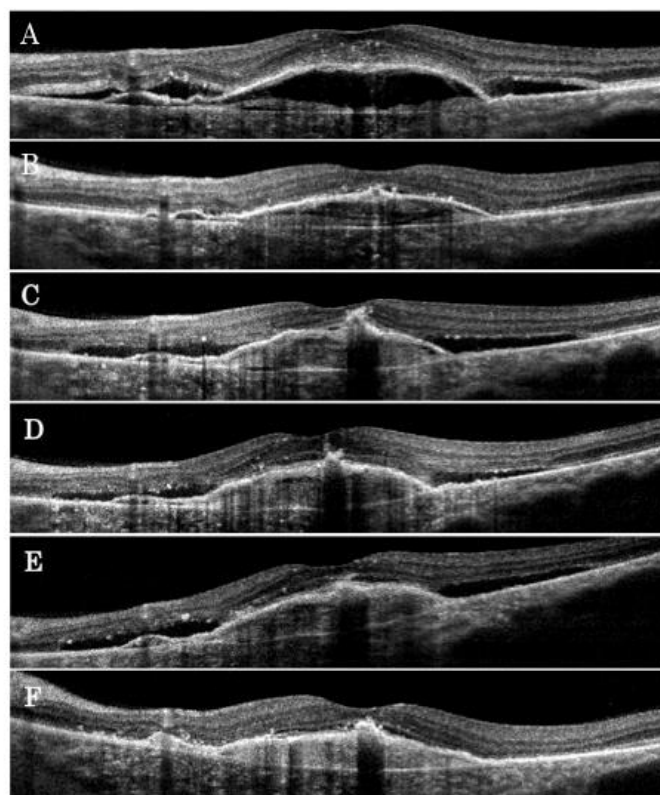
	PCV	Typical AMD	
		Classic component(-)	Classic component(+)
Subjects with tachyphylaxis	N=1	N=4	N=2
Initial non-responders	N=7	N=11	N=1
Responders	N=29	N=50	N=47

* $P=0.008$ (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
 88 and responders ($P=0.47$; chi-square test).

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



92

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

94 An 80-year-old man with typical AMD. A. At baseline, an OCT image shows type 1 CNV and a

95 serous retinal detachment (SRD) in the macular area. B. After 3 consecutive monthly intravitreal

96 injections of ranibizumab, no SRD is seen in OCT. C. After 7 injections of ranibizumab, an OCT

97 image shows recurrent SRD with 1.0 logMAR visual acuity. D. Therapy was switched to

98 pegaptanib injections, and SRD was decreased and the BCVA improved to 0.7 logMAR visual

99 acuity after 1 injection of pegaptanib. E. After 3 injections of pegaptanib, there was an increase in

100 SRD with 0.8 logMAR visual acuity. F. Therapy was switched to ranibizumab injections again,

101 and the SRD was resolved with 0.7 logMAR visual acuity following 1 ranibizumab injection.

102

103 **4. DISCUSSION**

104 In recent years, anti-VEGF drugs have been found to be effective for exudative AMD. These
 105 agents have been shown to prevent the deterioration of visual acuity or even improve visual
 106 acuity in AMD patients [3,11]. However, there are some patients who seem not to respond to the
 107 drug at all at the induction phase. We called those patients initial non-responders. We reported
 108 previously that 10.1% of AMD patients were initial non-responders [10]. On the other hand, there
 109 were other patients whose response to the drug seemed to decrease gradually after repeated
 110 treatments. We defined those cases as patients who developed tachyphylaxis.

111 The reason why tachyphylaxis occurs has not been completely explained yet. However, there
 112 are possibly some factors that play a role in the development of tachyphylaxis. Tachyphylaxis
 113 may occur because of neutralization of ranibizumab [3]. Ranibizumab is a humanized
 114 monoclonal antibody. However, repeated injections might induce neutralizing antibodies. Another
 115 mechanism could be upregulation of the receptors [12]. Because of upregulation of the receptors,
 116 the amount of intravitreal ranibizumab may not be enough to shut down the process. Another
 117 explanation could be upregulation of the production of VEGF by macrophages [13].
 118 Macrophages have been considered to induce the secretion of VEGF as well as retinal pigment
 119 epithelium cells. Another mechanism could be reactivation of the CNV driven by other pathways

120 such as ICAM-1, E-selectin, CD44 and basic and acidic fibroblast growth factors [14]. A change
121 in CNV is another possible cause for developing tachyphylaxis. Permanent structural damage to
122 the vascular walls of the CNV could result in abnormal vascular permeability and persistent
123 exudation [13]. To avoid a decrease in the effect of the drug because of tachyphylaxis, some
124 possible solutions have been reported. Tachyphylaxis can be reduced using combination therapy
125 and taking drug holidays. Less development of tachyphylaxis would be expected when using the
126 PRONT protocol than the repeated use of drugs [12].

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

135 The mechanism for having no response seems to be unlike that for tachyphylaxis. It is
136 considered that, in cases of initial non-responders, VEGF is not related to the pathophysiology of
137 AMD because an anti-VEGF drugs do not demonstrate an effect at the initial therapy. However,

138 patients with tachyphylaxis to ranibizumab might respond to other anti-VEGF drugs. Intravitreal
139 aflibercept has become an effective treatment for the patients with AMD [18]. Patients with
140 tachyphylaxis to ranibizumab may show a desirable response using treatment regimen with
141 aflibercept [19,20].

142 In conclusion, we found more patients who developed tachyphylaxis with occult CNV than
143 patients with other lesion types. In future trials, the mechanisms of the development of
144 tachyphylaxis need to be elucidated, and additional treatments to have ideal responses with anti-
145 VEGF therapy need to be developed.

146

147 **CONSENT**

148 Not applicable.

149

150 **ETHICAL APPROVAL**

151 Not applicable.

152

153 **COMPETING INTEREST**

154 Authors have declared that no competing interests exist.

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