·Letter to the Editor·

Tachyphylaxis during ranibizumab treatment of exudative age-related macular degeneration

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Dear Editor,

We are intestigators from Turkey primarily studying exudative age-related macular degeneration (AMD). Here we present the results of our retrospective clinical study on tachyphylaxis development during the treatment of exudative AMD with ranibizumab, which, we believe, will form a basis for further prospective studies to predict the drug response in anti-vascular endothelial growth factor (anti-VEGF) treatment.

Before the introduction of effective therapy, exudative AMD was the leading cause of blindness among the elderly population in developing and developed countries [1-4]. The anti-VEGF therapy, such as ranibizumab and bevacizumab is the latest approach for treating this disease and dramatically changed the prognosis of exudative AMD. With the increasing use of ranibizumab and bevacizumab for exudative AMD, a growing need is observed for understanding their long-term effects. For long-term medication, a reduction in their biological effect is a major concern, as it can limit long-term efficacy. This is known as tachyphylaxis or tolerance [5]. A number of studies have suggested that tachyphylaxis develops during the intravitreal anti-VEGF treatment of AMD lesions[6-8].

We aimed to investigate whether tachyphylaxis develops during the treatment of exudative AMD with ranibizumab and determine the rate and main characteristics of patients who developed tachyphylaxis after ranibizumab treatment.

A total of 273 eyes of 255 patients were treated for exudative AMD in a university clinic from September 2009 to April 2012. These patients had received intravitreal ranibizumab and had optical coherence tomography (OCT) of the macula at each visit. Eyes that did not respond to treatment initially (31/273 eyes, 11.4%; *i.e.* nonresponder from the beginning) and those who had a missed scheduled visit and treatment (31/273 eyes, 11.4%) and eyes that had polypoidal choroidal vasculopathy (PCV) or retinal angiomatous proliferation (RAP; 5/273 eyes, 1.8%) were excluded from the study. A total of 206 eyes of 201 patients met these criteria. Patients gave written informed consent to participate in the study. The study was approved by the Institutional Ethics Committee and conducted according to the Declaration of Helsinki.

For ophthalmological examination, we determined the best-corrected visual acuity (BCVA) using an ETDRS chart, and the logMAR scale was used for comparisons. In addition, slit-lamp biomicroscopy, central retinal thickness (CRT), and pigment epithelial detachment (PED) height by OCT (OCT status, Carl Zeiss Meditec, Dublin, CA, USA), color fundus photography, and fluorescein angiography (before treatment and when needed in subsequent indeterminate cases) (Topcon Imagenet i-base, Japan) were performed. Examinations were conducted before treatment and monthly thereafter. In the loading phase, ranibizumab (0.5 mg/0.05 mL; using a 30-G needle) was injected once per month in 3 doses. Below treatments were given when lesion was assessed as an active lesion. All retreatments were performed using ranibizumab. Lesion activity was assessed using changes in BCVA, CRT in OCT, presence and amount of hemorrhage associated with the lesion, change in lesion size, and fluorescein angiography staining pattern. An eye with an active lesion was described as one with a visual acuity loss of at least 5 letters with OCT evidence of intraretinal/subretinal fluid in the macula or an increase in the CRT or PED height in OCT or a new macular hemorrhage associated with the lesion or an increase in the lesion size with evidence of late leakage of the lesion on fluorescein angiography. The presence and extent of these exudation features were evaluated at each visit by inspecting the individual B-scans and measuring the CRT or PED height using the OCT instrument from approximately the same retinal location. If PED was present, the maximum height (μm) of the PED on OCT was determined using the retinal thickness analysis protocol and built-in manual calipers.

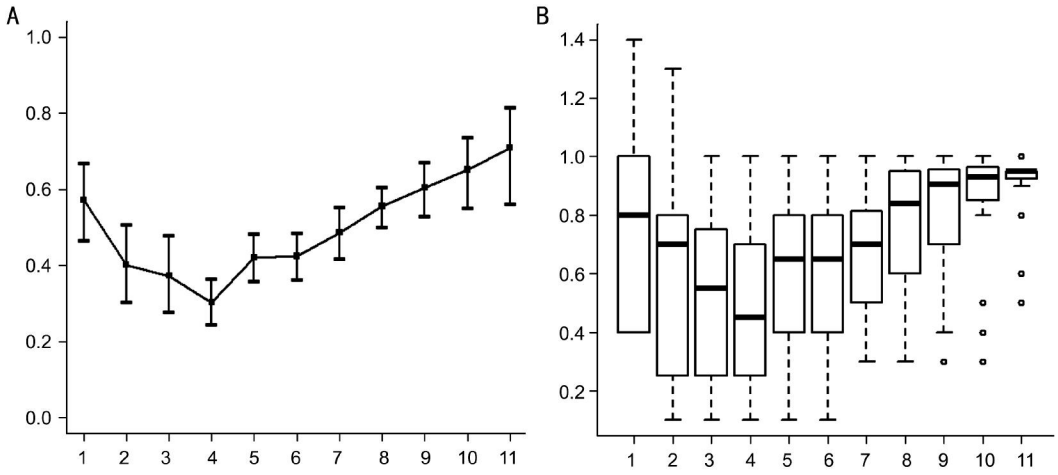

Figure 1 BCVA measurements over the course of the study A: Relative treatment effects with 95% CI; B: Box plot distribution.

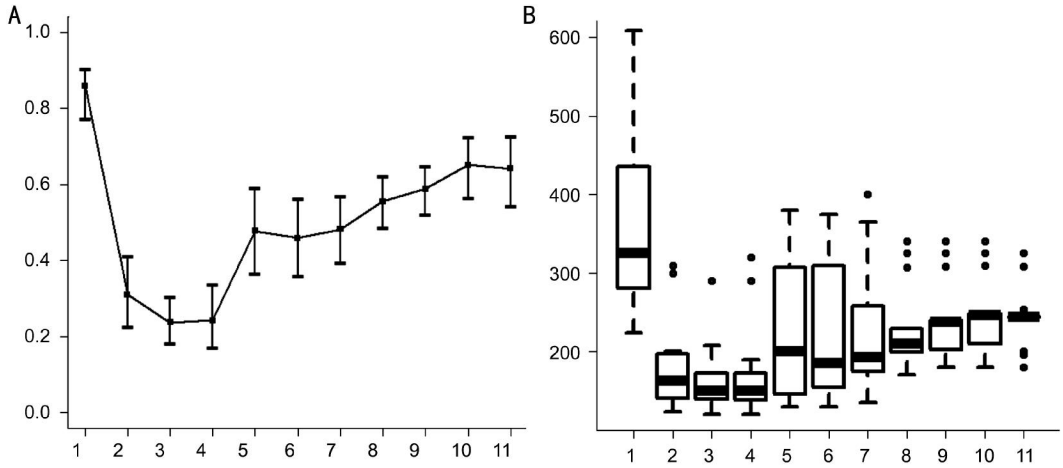

Figure 2 CRT measurements over the course of the study A: Relative treatment effects with 95% CI; B: Box plot distribution.

We defined tachyphylaxis as evidence of an initial positive response (reduction in CRT or PED height) to treatment with intravitreal injections, followed by an eventual poor response to treatment (increase in CRT or PED height), despite at least 2 more monthly injections after the loading phase. Hence, stabilization of CRT or PED height during treatment was not considered as tachyphylaxis.

For each eye that showed evidence of tachyphylaxis, the following parameters were analyzed: age, gender, angiography choroidal neovascularization (CNV) lesion classification at the time of the initial intravitreal injection, number of treatments with ranibizumab before developing tachyphylaxis, and BCVA and OCT findings (CRT and PED height) at each visit.

We found that 16 eyes of 16 patients (16/206 eyes, 7.77%) met the criteria for tachyphylaxis. None of the patients with tachyphylaxis received treatment for both eyes. There were 11 (68.75%) males and 5 (31.25%) females, with a mean age of 73.69±7.84y. Occult type CNV lesion was present in 10 (62.50%) patients, and classic type was present in 6 (37.50%). None of the patients had received any prior treatment (anti-VEGF or photodynamic therapy) for exudative AMD. The mean follow-up of the whole population was 22.1±8.1mo; the median number of injections during follow-up was 9 (range: 5-18). The median number of injections before developing tachyphylaxis was 4 (range: 2-16).

The median BCVA at baseline was 0.80 (range: 0.4-1.4) logMAR. This decreased to 0.45 (range: 0.1-1) at the last visit before developing tachyphylaxis, increased to 0.65 (range: 0.1-1) at the time of tachyphylaxis development, and was 0.85 (range: 0.5-1) at the last visit. Effect of time on the BCVA results was statistically significant (P<0.001; Figure 1).

At baseline, the median CRT was 325 (range: 224-609) μm. At the last visit before tachyphylaxis development, the median CRT was 150 (range: 120-320) μm. This increased to 200.5 (range: 130-380) μm at the visit when tachyphylaxis was noted and was 227 (range: 180-325) μm at the last visit. Effect of time on the CRT results was statistically significant (P<0.001; Figure 2).

At baseline, the median PED height in patients with PED was 384 (range: 80-850) μm. This was 0 (range: 0-240) μm at the last visit before development of tachyphylaxis, increased to 80 (range: 0-580) μm at the visit when tachyphylaxis was noted, and was 192 (range: 70-311) μm at the last visit. Effect of time on the PED results was statistically significant (P <0.001; Figure 3).

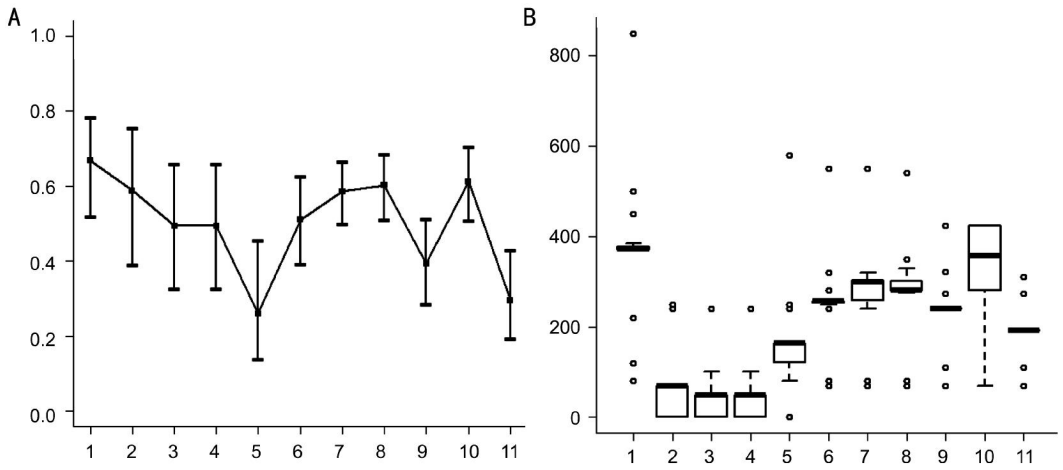

Figure 3 PED height measurements over the course of the study A: Relative treatment effects with 95% CI; B: Box plot distribution.

Theoretically, several factors could play a role in tachyphylaxis/tolerance. For example, receptors may adapt to the long-term use of anti-VEGF by reducing their sensitivity to the drug [5]. The decrease in the efficacy of the drug may also be explained by the development of a systemic immune response with neutralizing antibodies, which is known as pharmacokinetic tolerance and can be expected with chronic use [9]. Another possible cause of a decrease in the biological response may be an increase in other angiogenic factors, such as fibroblast growth factor, to compensate for blocked VEGF activity[10]. Tachyphylaxis may also develop because the basic nature of CNV has changed, such as a change in CNV lesion type, the associated loss of retinal pigment epithelium function, the development of chronic inflammatory changes, or maturation of the target abnormal vessels[10-12].

We observed that some patients developed a decreased response quickly after 2 or 3 anti-VEGF injections, while others did not develop tachyphylaxis until after 10-16 injections. Schaal *et al* [7] reported that approximately 3 injections were required before efficacy decreased to 50% of the initial OCT response. Forooghian *et al* [8] found that the median number of intravitreal bevacizumab treatments before developing tachyphylaxis was 8. In our study, the median number of intravitreal treatments before developing tachyphylaxis was 4. A decrease in the response may possibly be explained by 2 different mechanisms: one occurring earlier (after 2 or 3 injections) may be known as tachyphylaxis and the one occurring later (after 10 or more injections) may be known as tolerance. Binder [5] stated that tachyphylaxis could develop relatively rapidly when drugs are used repeatedly over a short period, while tolerance is characterized by a slow loss of efficacy over time. It may be important to differentiate more clearly between tachyphylaxis and tolerance so as to improve treatment strategies, for example, to increase the dosage or shorten treatment intervals if tolerance develops or interrupt treatment if tachyphylaxis occurs[5].

In conclusion we demonstrated the development of a decreased therapeutic response over time in eyes with CNV treated with ranibizumab. This diminished response may be tachyphylaxis/tolerance. Awareness of this possible effect with monotherapy in exudative AMD is important in the long-term management of patients with CNV.

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