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"TREAT AND EXTEND" DOSING OF INTRAVITREAL ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY FOR TYPE 3 NEOVASCULARIZATION/RETINAL ANGIOMATOUS PROLIFERATION

MICHAEL ENGELBERT, MD, PHD,*† SANDRINE A. ZWEIFEL, MD,*†‡
K. BAILEY FREUND, MD*†

Purpose: The purpose of this study was to analyze long-term outcomes for the treatment of type 3 neovascularization/retinal angiomatous proliferation using a "Treat and Extend" dosing regimen for antivascular endothelial growth factor therapy.

Methods: This was a retrospective analysis of visual acuity and optical coherence tomography data of 11 eyes of 10 consecutive patients with newly diagnosed type 3 neovascularization/retinal angiomatous proliferation treated with intravitreal bevacizumab and/or ranibizumab with at least a 12-month follow-up. Three monthly injections were followed by continued treatment at intervals increasing by 2 weeks per visit, to a maximum of 10 weeks, unless clinical or optical coherence tomography evidence of persistent or recurrent fluid was present, in which case, the interval was shortened.

Results: Mean baseline Snellen visual acuity was 20/80, improved to 20/40 at 1 month, and was maintained throughout the 36-month period (n = 11 at 12 months, n = 10 at 24 months, and n = 8 at 36 months) ($P < 0.04$, paired *t*-test). The mean center point optical coherence tomography thickness decreased from 320 μm to 180–230 μm, and was maintained during the study period ($P < 0.02$). The mean number of injections was seven in the first year, six in the second year, and seven in the third year.

Conclusion: "Treat and Extend" antivascular endothelial growth factor dosing in type 3 neovascularization/retinal angiomatous proliferation delivers promising outcomes at a reduced burden for the patient and health care system compared with monthly and optical coherence tomography-guided dosing regimens.

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Type 3 neovascularization (otherwise known as retinal angiomatous proliferation [RAP])[1,2] is a subtype of neovascular age-related macular degeneration (AMD) with distinct angiographic and optical coherence tomography (OCT) features related to intraretinal proliferation of the abnormal vessels with associated retinal–retinal and retinal–choroidal anastomosis. Its natural course is typically worse than other more frequent lesion types such as subretinal pigment epithelium neovascularization (type 1)/occult choroidal neovascularization or subneurosensory neovascularization (type 2)/well-defined (classic) choroidal neovascularization.[3–5] Many different treatment strategies[6] such as photocoagulation,[3,4,7] transpupillary thermotherapy,[3,8] photodynamic therapy (PDT),[9–13] intravitreal antivascular endothelial growth factor (anti-VEGF) agents,[6,14,15] intravitreal triamcinolone acetonide, surgical excision,[16,17] and many combinations of the above[18–21] have been tried in small case series with limited follow-up.

Monthly injections of antiangiogenic agents have become the standard of care for the treatment of neovas-

From the *LuEsther T. Mertz Retinal Research Center, Manhattan Eye, Ear and Throat Hospital; †Vitreous-Retina-Macula Consultants of New York, New York, New York; and ‡University Hospital Zurich, Department of Ophthalmology, Frauenklinikstrasse 24, 8032 Zurich, Switzerland.

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Reprint requests: K. Bailey Freund, MD, 460 Park Avenue, 5th Floor, NY 10022; e-mail: kbfny@aol.com

cular AMD[22,23] but are expensive and difficult to sustain in this elderly patient population. However, the less frequent dosing in the PIER trial,[24] in which patients received quarterly injections after an initial series of three monthly injections, could not reproduce the excellent results obtained in trials using monthly dosing. The PrONTO Study[25,26] attempted to tailor the dosing to the individual needs of the patient based on acuity decline, clinical findings, or OCT evidence of disease activity and was able to demonstrate good visual results after a >24-month period.

Although PrONTO-style dosing has become widely adopted in the retinal community and seems to yield favorable results, this strategy does require monthly visits, clinical examinations, and OCTs with patients uncertain if or when they will need treatment. Because eyes with type 3 neovascularization/RAP typically manifest retinal–choroidal anastomosis, recurrent exudation may occur earlier and more frequently than with other neovascular lesion types. In our experience, some patients managed with this strategy will return for assessments having already developed macular hemorrhages in the injection-free interval with irreversible vision loss.[27–29] In theory, a dosing regimen that does not maintain the macula in a "dry" state could deny some patients the opportunity for further visual recovery.

The "Treat and Extend" dosing regimen is a strategy intended to resolve macular exudation and maintain the macula in this "dry" state indefinitely with, when possible, fewer patient visits and treatments than monthly dosing.[30,31] The strategy consists of an initial induction or "loading" sequence of at least three monthly injections. If stable visual acuity, an absence of macular hemorrhage, and a dry OCT have been achieved at this point, patients continue to receive regular maintenance injections at increasing intervals. At 6 weeks after the last of the three monthly injections, visual acuity, clinical findings, and OCT changes are recorded again, and patients receive an injection regardless of the presence or absence of disease activity. However, the interval to the next visit (and scheduled injection) is based on an observed change in the above parameters. If there are no changes, the next visit is scheduled for 8 weeks later. If there is a change, the patient comes for another scheduled injection and examination after 4 weeks. The observation and scheduled treatment interval is extended (hence the term "Treat and Extend") to a maximum of 10 weeks. We report on 11 eyes of 10 patients with type 3 neovascularization/RAP managed with the "Treat and Extend" dosing regimen and with follow-up of between 12 and 36 months.

Materials and Methods

A waiver of authorization for use of protected health information for the above-referenced research and a waiver of consent for this retrospective chart review were obtained from the Institutional Review Board committee of the Manhattan Eye Ear and Throat Hospital, New York, NY.

The diagnosis of type 3 neovascularization/RAP was made by the treating physician (K.B.F.) based on the characteristic clinical, OCT, and angiographic features including intraretinal hemorrhage, cystoid macular edema, intraretinal vascular anastomosis, retinal–choroidal anastomosis, and in some cases, the presence of pigment epithelial detachment (PED) on OCT. Patients treated previously with thermal laser, PDT, or intravitreal pegaptanib (Macugen, Pfizer Inc., New York, NY), or who presented with subfoveal fibrosis or atrophy, a history of vitrectomy, aphakia or absence of posterior capsule, history of idiopathic or autoimmune associated uveitis in either eye, or diabetic retinopathy more severe than mild nonproliferative stage, were excluded from this study. Patients with preexisting cardiac or cerebrovascular conditions were not excluded from the study.

The treatment consisted of intravitreal injection of 1.25 mg of bevacizumab (Avastin, Genentech Inc., South San Francisco, CA) or 0.5 mg ranibizumab (Lucentis, Genentech Inc.) suspended in 0.05 mL. For the purpose of this analysis, no distinction between either antiangiogenic drug was made. Before intravitreal injection, topical anesthesia and surface disinfection with 5% povidone–iodine was performed. Intravitreal injections were administered at the time of diagnosis and subsequently followed a protocol we termed "Treat and Extend." Patients all received at least 3 monthly injections followed by continued treatment at intervals increasing by 2 weeks per visit once visual acuity was stable, OCT showed an absence of intra- and subretinal fluid, and all hemorrhage had resolved. Resolution of PED was not required before treatment intervals were lengthened. The treatment interval was extended to a maximum of 10-week "maintenance" unless clinical examination or OCTdetected new hemorrhage or persistent/recurrent fluid. In those cases, the interval was shortened by 2 weeks and maintained at that duration, provided this resolved the fluid.

The main outcome measure in this study was visual acuity after treatment. Decrease in retinal thickness, number of injections needed, and change in funduscopic or tomographic appearance were assessed as well.

Snellen visual acuity was measured by a certified ophthalmic technician. Snellen acuity was converted into logarithm of the minimum angle of resolution (logMAR) for statistical analysis at baseline and at 1, 3, 12, 24, and 36 months after injection of an antiangiogenic agent. Changes in logMAR-converted acuities were tested with a paired Student's *t*-test and accepted as significant if $P < 0.05$. Also, the proportions of patients

approximately halving (≥0.3 logMAR, but <0.6 logMAR-converted Snellen visual acuity improvement) or approximately quartering their visual angle (≥0.6 logMAR-converted Snellen visual acuity improvement), as well as those that remained stable (<0.3 logMAR-converted visual acuity improvement) or lost lines on the Snellen chart compared with baseline, were reported.

The quantitative assessments of center point retinal thickness were made using Stratus OCT (Carl Zeiss Meditec, Dublin, CA) and Topcon OCT (Topcon 3D OCT-1000, Topcon Medical Systems, Paramus, NJ). The center point retinal thickness was defined as the distance between the internal limiting membrane and the retinal pigment epithelium under the fovea and did not include any fluid under the retinal pigment epithelium. For Topcon OCT images, the calipers provided by the Topcon image analysis software were used. The Stratus OCT measurements were made manually on the IMAGEnet software on a single horizontal line scan through the fovea (Topcon Medical Systems), and the calculated data in pixels were multiplied with a conversion factor of 8 μm/pixel. This conversion factor had been derived from previous comparisons of controls on the different imaging platforms (based on 20 normal eyes measured on the 2 platforms, Howard F. Fine, personal communication).

The qualitative assessment included identification of intraretinal cysts, neovascular complex within the retinal layers, and PED. Additional funduscopic and tomographic changes and their development over time were recorded as well. Specifically, the presence of intraretinal hemorrhage or development of a pigment epithelial rip on funduscopy and the presence of intra- or subretinal fluid or PED on high-resolution B-scans were determined. Because staging of type 3 neovascularization/RAP is difficult and of controversial significance, this was not performed.

Results

Eleven eyes of 10 patients were included in this study. Eleven eyes completed the 12-month follow-up, 10 eyes completed the 24-month follow-up, and 8 eyes completed the 36-month follow-up.

Patient demographics, baseline, and follow-up visual acuity, center point retinal thickness data, and number of injections in the first, second, and third year are presented in Table 1. Median patient age was 85 years (range, 71–92 years). Seven of 10 patients were women. Two contralateral eyes had evidence of antecedent type 3 neovascularization/RAP lesions, and 2 patients developed disease in the contralateral eye during the study period. Only one of these two latter eyes was treated with a "Treat and Extend" protocol and included

Table 1. Summary of Patient Data

			Baseline						Second			Third	
Patient	Gender	Age (Years)	Baseline VA	OCT (μm)	Month 1 VA	Month 1 OCT (μm)	Month 12 VA	Month 12 OCT (μm)	Month 12 No Inj	Month 24 VA	Month 24 OCT (μm)	Year No Inj	Month 36 VA	Month 36 OCT (μm)	Year No Inj	RAP in Fellow Eye
1 OD	F	89	20/400	257	20/160	299	20/100	174	5	20/200	174	5	20/80	181	6	P
2 OS	F	85	20/50	241	20/50	183	20/60	150	6	20/40	177	5	20/40	163	7	P
3 OD	F	84	20/25	246	20/25	192	20/25	186	9	20/25	117	10	—	—	—	P
3 OS	—	—	20/200	433	20/40	289	20/25	118	10	20/30	108	8	20/40	136	10	L
4 OS	F	83	20/80	282	20/30	199	20/20	166	7	20/25	174	5	—	—	—	—
5 OS	M	92	20/200	410	20/70	174	20/100	232	7	—	—	—	—	—	—	L
6 OS	M	71	20/20	182	20/25	133	20/25	121	8	20/20	174	8	20/20	134	6	—
7 OS	F	76	20/50	548	20/30	374	20/50	254	6	20/30	196	5	20/30	199	7	—
8 OD	F	92	20/30	200	20/40	224	20/40	216	6	20/25	224	6	20/30	225	6	—
9 OS	M	82	20/200	388	20/70	206	20/40	315	6	20/40	224	6	20/40	218	5	—
10 OS	F	91	20/70	336	20/40	246	20/50	166	8	20/60	175	7	20/50	197	7	—

Inj, injections; P, at presentation; L, later.

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