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Treatment of Non-neovascular Idiopathic Macular Telangiectasia Type 2 with Intravitreal Ranibizumab: Results of a Phase II Clinical Trial

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Abstract

Purpose—To evaluate the safety and preliminary efficacy of intravitreal ranibizumab for non-neovascular idiopathic macular telangiectasia, type 2 (IMT2).

Methods—Single-center, open-label phase II clinical trial enrolling 5 participants with bilateral non-neovascular IMT2. Intravitreal ranibizumab (0.5mg) was administered every 4 weeks in the study eye for 12 months with the contralateral eye observed. Outcome measures included changes in: best corrected visual acuity (BCVA), area of late-phase leakage on fluorescein angiography (FA), and retinal thickness on optical coherence tomography (OCT).

Results—The study treatment was well-tolerated and associated with few adverse events. Change in BCVA at 12 months was not significantly different between treated study eyes (0.0 ± 7.5 letters) and control fellow eyes ($+2.2 \pm 1.9$ letters). However, decreases in the area of late-phase FA leakage ($-33 \pm 20\%$ for study eyes, $+1 \pm 8\%$ for fellow eyes) and in OCT central subfield retinal thickness ($-11.7 \pm 7.0\%$ for study eyes and $-2.9 \pm 3.5\%$ for fellow eyes) were greater in study eyes compared to fellow eyes.

Conclusions—Despite significant anatomical responses to treatment, functional improvement in visual acuity was not detected. Intravitreal ranibizumab administered monthly over a time course of 12 months is unlikely to provide a general and significant benefit to patients with non-neovascular IMT2.

Keywords

anti-VEGF; clinical trial; idiopathic macular telangiectasia; IMT2; MacTel; ranibizumab

INTRODUCTION

Idiopathic macular telangiectasia, also known as idiopathic juxtafoveal or perifoveal telangiectasia, causes progressive metamorphopsia and deterioration of central visual function that can lead to blindness. Systematically described by Gass and Blodi¹, its structural categorization has been more recently simplified by Yannuzzi² into two subtypes – type 1, the unilateral aneurysmal form, and type 2, the bilateral perifoveal telangiectatic form. Idiopathic macular telangiectasia type 2 (IMT2) is an uncommon disorder with separate studies estimating its prevalence ranging from approximately one in 1,000 to five in 100,000 people.^{3, 4}

Clinical characteristics of IMT2 include retinal opacification, retinal vascular changes (telangiectasias, right angle venules, and retinal neovascularization), intraretinal crystalline deposits, and retinal pigment epithelial (RPE) cell hypertrophy and migration.⁵ Multimodal imaging of IMT2 using fluorescein angiography (late-phase leakage), fundus autofluorescence (foveal hyperautofluorescence), OCT (foveal atrophy or cystic change), and microperimetry (foveal/parafoveal scotomata), has also revealed other anatomic and functional changes in the natural history of the disease.⁶

The etiology and pathogenetic mechanisms underlying IMT2 are not well understood.⁷ Histopathological studies by Powner et al⁸ have characterized retinal cell degeneration, particularly that affecting Müller cells, as a key pathologic feature in the disease. Several other studies have also described histopathological abnormalities in retinal vessels, including vascular ectasia as well as pericyte and endothelial cell degeneration.^{9, 10} These findings, together with clinical signs of abnormal vascular permeability, have suggested the possibility that elevated intraocular levels of vascular endothelial growth factor (VEGF), a factor highly influential in retinal vascular diseases, may play a role in the disease pathogenesis of IMT2.¹¹

While there is currently no proven effective treatment or prevention for IMT2, multiple case reports and small, retrospective case series have previously reported clinical benefit with anti-VEGF inhibition in this clinical indication.^{12–16} Several of these studies have described a beneficial treatment effect with bevacizumab, a recombinant, humanized monoclonal antibody that binds to all human VEGF-A isoforms, particularly in the proliferative neovascular stage of IMT2.¹⁷ Prospective studies using bevacizumab for non-neovascular IMT2, however, have reported mixed results.^{18–20} Additionally, recent case reports have described the use of ranibizumab, a 48kDa antigen-binding fragment of bevacizumab, in the treatment of IMT2.^{21–25} Based on preliminary data describing the efficacy of anti-VEGF agents in the treatment of IMT2, the current study was performed to evaluate the safety and efficacy of monthly intravitreal ranibizumab in the treatment of non-neovascular IMT2.

METHODS

Study Design

This prospective, single-center, open-label, non-randomized study consecutively enrolled five participants with bilateral IMT2 without evidence or history of neovascular change.

Participants were enrolled at the National Eye Institute (NEI), National Institutes of Health (NIH) between February 2009 and October 2009. The research was supported by the Intramural Research Program, NEI (contract N01-EY-7-0001). The study protocol and informed consent forms were approved by an institutional review board, and the study was registered at www.clinicaltrials.gov (NCT00685854).

Inclusion criteria for enrollment were the following: at least 18 years of age, clinical signs of IMT2 bilaterally, and visual acuity of at least 20/400 in either eye. Patients with evidence or history of retinal neovascular changes in either eye, history of severe cardiovascular disease in the preceding five years, history of stroke in the past year, active ocular or periocular infection, history of intravitreal drug injections, or a history of vitrectomy, glaucoma filtering, or corneal transplant surgery in either eye, were not enrolled. The study eye was designated as the eye with the greater severity of involvement, as determined by visual acuity measurements, fluorescein angiography, and OCT results. However, in cases where the more severely affected eye was judged unlikely to benefit from treatment due to irreversible structural changes (extensive atrophy or pigmentary change, chronic macular scarring), then the less severely affected eye was considered the study eye.

After the baseline enrollment visit, all participants completed 13 additional study visits (visits 1 to 13), with a four-week interval between visits. Participants were scheduled to receive an intravitreal injection of 0.5mg ranibizumab (Genentech, South San Francisco, CA) in one eye (hereafter referred to as the “study eye”) at the baseline visit and at each of the subsequent 13 visits. The contralateral eye (hereafter referred to as the “fellow eye”) was observed without treatment. If a participant did not demonstrate any structural or functional response after the first four monthly injections in the study eye, subsequent injections could be withheld. Injections could also be withheld at any visit for safety considerations, per the discretion of the study physician. Otherwise, participants were scheduled to receive monthly treatment at the same dose and schedule through week 52 (visit 13). Participants were also assessed at a follow-up exam (visit 14) eight weeks after the final study injection at week 52 (visit 14).

Ocular and systemic evaluations and study outcome measures

Participants were evaluated at baseline and the final study visit with a physical examination, medications assessment, and assessment of medical history. At each visit, participants were evaluated with a complete ophthalmic examination, which included bilateral assessment of best-corrected visual acuity (BCVA), stereoscopic funduscopy, color fundus photography (CFP), fluorescein angiography (FA), fundus autofluorescence imaging (FAF), and spectral domain optical coherence tomography (SD-OCT). Microperimetry (MP1) was performed at baseline, week 12 (visit 3), week 36 (visit 8), and week 52 (visit 13).

Best corrected distance visual acuity was assessed using a standard Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol and scored in terms of the number of ETDRS chart letters read. Color fundus photography (CFP) and fluorescein angiography (FA) were performed using a standard digital imaging system (OIS, Sacramento, CA). FAF images were captured with a confocal laser scanning ophthalmoscope (HRA2, Heidelberg Engineering, Heidelberg, Germany) using an excitation wavelength of 488nm and a barrier

filter at 500nm. SD-OCT images were captured with the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) using the 512×128 scan pattern with the center of the 6×6mm scanning area positioned at the foveal center. Using the packaged software, longitudinal OCT scans for each eye were automatically aligned, manually checked, and realigned if necessary. Thickness analyses on OCT were performed using a circular ETDRS-type grid centered on the fovea. Measurements of the full thickness of the neuroretina were assessed for the central region (circle of diameter 1mm), as well as the 4 “inner” quadrants, which were circumscribed by a circle of diameter 3mm, concentric to the central region and divided into superior, inferior, nasal, and temporal quadrants. Microperimetry testing was performed using the MP1 microperimeter (NAVIS software version 1.7.1, Nidek, Padua, Italy). The following test configuration was used: Retinal sensitivity was calculated with a background luminance of 4 apostilbs (1.27 cd/m²) using a 68-loci circular grid centered on the center of the macula covering the central 20° of the macula (10-2 program). A testing stimulus of size Goldmann III (area of 4mm², diameter 0.4°) was used with a stimulus duration of 200ms. A 4-to-2 staircase strategy was employed using decreasing stimulus intensities ranging from 127 to 2.54 cd/m², which correspond to retinal sensitivities of 0 to 20 dB, respectively. The follow-up testing feature in the packaged software was employed.

The primary outcome measure of the study was the change in best-corrected visual acuity (BCVA) at one year relative to baseline, compared between study eye and fellow eye. Other outcome measures included the change in area of late-phase leakage on FA, change in retinal thickness as measured by SD-OCT, change in the area of hypofluorescent pigment clumping as measured by FAF, and change in retinal sensitivity as measured by microperimetry. The area of late-phase leakage on FA was measured by two independent graders (BT and EK) using computer-guided measurement tools available in the digital fundus photograph viewer software program (OIS, Sacramento, CA). Two repeat measurements were made by each grader and all four individual measurements were then averaged. When the averages from the two graders in any given case differed by more than 20%, adjudication by a third grader (WW) was obtained. Changes in retinal sensitivity were categorized by spatial location prior to analysis. A subset of tested points was identified as “points in the area of leakage” by their location within or adjoining the area of late-phase fluorescein leakage based on the superposition of the testing grid over an aligned image of the late-phase angiogram captured at study baseline. This categorization of points using the baseline image provided information about the effect of late-phase FA leakage on retinal sensitivity at baseline; furthermore, changes in the leakage pattern over time were reflected in retinal sensitivity changes in the subset of baseline leakage points.

RESULTS

Baseline Patient Demographics and Ocular Characteristics

All five participants were enrolled in the study between Feb 18, 2009 and Oct 21, 2009. Table 1 summarizes the baseline demographic and ocular information for the five participants. Statistical analyses did not reveal any significant differences at baseline between the study and fellow eyes for any of the examined ocular parameters (visual acuity,

retinal thickness on OCT in the central subfield, and area of late-phase leakage on FA; paired t-test, $p>0.05$ for all comparisons).

Of the five study participants, three participants received 14 (out of 14 possible) scheduled injections in the study eye, each given four weeks apart. Two participants received a total of 13 scheduled injections; an injection was deferred in participant #2 at visit 8 and in participant #3 at visit 10 owing to participant reports of subjective and mild symptoms of visual difficulty that were transient in nature. On both occasions when injection was withheld, no significant objective changes in visual acuity were noted, and no adverse ocular changes were recorded on clinical examination. In both participants, injections were resumed at the subsequent visit. One participant (#5) elected to have cataract extraction and intraocular lens implantation in the fellow eye two weeks prior to visit 8. Changes in the grading of the cataract severity in this eye from baseline were not observed prior to surgery.

Ocular and Systemic Safety of Intravitreal Ranibizumab

No serious adverse events were noted in the study. A total of 27 adverse events were recorded during the study, all of which were mild or moderate in severity. Only four events were ocular in nature and judged to be related to the study treatment, including eye soreness, mild chemosis, and corneal abrasion which were reported in one participant each. These were more likely related to the procedure of intravitreal injection, rather than to the study drug specifically.

Effect of Intravitreal Ranibizumab on Best Corrected Visual Acuity (BCVA)

The primary objective of this study was to investigate the effect of intravitreal ranibizumab on change in BCVA (in terms of ETDRS letters). Figure 1A shows the change in visual acuity from baseline in all five study and all five fellow eyes at each study visit (visits 1 through 14). At the end of the treatment period (visit #13), three out of five study eyes (in participants #3, #4, #5) recorded a net increase in visual acuity, versus four out of five fellow eyes (in participants #1, #2, #3, #5). These visual acuity changes were generally small, and only one study eye exhibited a visual acuity increase from baseline that was greater than 10 letters (participant #4). Figure 1B shows the mean change in BCVA from baseline for study and fellow eyes at each study visit (visits 1 to 13) and the final safety visit (visit 14). By the end of the treatment period (visit 13), the mean change in visual acuity from baseline was 0.0 ± 7.5 letters for study eyes and $+2.2\pm1.9$ letters for fellow eyes. For both study and fellow eyes, mean visual acuity after one year of treatment (visit 13) was not significantly different from that at baseline ($p>0.05$, paired t-test). Change in mean visual acuity from baseline also did not differ significantly between study and fellow eyes at any visit time point ($p>0.05$ for all comparisons, paired t-tests).

Effect of Intravitreal Ranibizumab on Fluorescein Angiography (FA) Late-Phase Leakage

In study eyes, a marked decrease in the area of late-phase leakage was observed at all visits following baseline (Figure 2). The area of leakage was either stable or increasing in untreated fellow eyes during the course of the study for all five participants (Figure 2A). In the fellow eye of participant #5, a large and marked increase in leakage area was observed following cataract extraction, which was likely attributable to the surgical procedure itself.

Due to the large magnitude of this effect, mean values for leakage area were computed omitting the data from participant #5 (Figure 2B). Significant differences in leakage area between study and fellow eyes were apparent following one ranibizumab injection (visit 1, $p=0.03$, paired t-test) and increased to a maximum after four to five treatments. The treatment effect remained stable with repeated injections during the course of the study. At the final study visit (visit 13), the mean change in late-phase FA leakage area was $-33\pm 20\%$ for study eyes and $+1\pm 8\%$ for fellow eyes. Following cessation of monthly treatments, leakage in study eyes at the final safety visit (visit 14, eight weeks following the injection at visit 13) increased by $15.3\pm 16.3\%$ relative to the preceding visit, suggesting a rebound effect without sustained treatment. The effect of treatment on the reduction in late-phase leakage in study eyes relative to fellow eyes is illustrated in Figure 3A.

Effect of Intravitreal Ranibizumab on Retinal Thickness as Measured by Optical Coherence Tomography (OCT)

The effect of intravitreal ranibizumab on total retinal thickness in foveal and parafoveal regions as measured with OCT was investigated as an outcome measure, as shown in Figure 4. Retinal thickness in the central subfield generally decreased from baseline during follow-up in study eyes, while either remaining stable or increasing in fellow eyes (Figure 4A). In the fellow eye of participant #5, a large and marked increase in retinal thickness was observed following cataract extraction, and this was again likely attributable to the surgical procedure itself. The mean reduction in retinal thickness in the central subfield, omitting the data from participant #5, was significantly larger in study eyes compared to fellow eyes (Figure 4B), reaching statistical significance following only one injection (visit #1, $p=0.03$, paired t-test). By the end of treatment (visit 13), the mean change in OCT central retinal thickness was $-11.7\pm 7.0\%$ for study eyes and $-2.9\pm 3.5\%$ for fellow eyes. Decreases in retinal thickness were also noted in all four parafoveal quadrants, although mean decreases in retinal thickness tended to vary according to location in the order: central = temporal > nasal > superior = inferior (Figure 4C–F). The effect of treatment on the OCT retinal thickness in study eyes relative to fellow eyes is illustrated in Figure 3B.

Effect of Intravitreal Ranibizumab on Retinal Sensitivity as Measured by Microperimetry (MP1)

The effect of intravitreal ranibizumab on retinal sensitivity as measured by microperimetry was also investigated in this study. Figure 5A illustrates the MP1 stimulus grid as overlaid on a color fundus image, demonstrating the fundus locations of tested stimulus points. A subset of tested points was identified as “points in the area of leakage” by their location within or adjoining the area of late-phase fluorescein leakage upon superposition of the testing grid over a co-registered image of the late-phase angiogram captured at study baseline (Figure 5B). The same subset of points was analyzed as “points in the area of leakage” at all subsequent study visits. Figure 5C and 5D depict the change in retinal sensitivity from baseline at each of the three study visits where MP1 data was collected (visits 3, 9, and 13). Participant #5 demonstrated a large increase in retinal sensitivity in the fellow eye following cataract extraction and intraocular lens placement prior to visit 8, likely secondary to increased light transmission status-post removal of the lens opacification. The mean change in retinal sensitivity from baseline for all stimulus points (Fig. 5E) and for the

subset of stimulus points in the area of leakage (Figure 5F) were calculated excluding participant #5. At the end of treatment (visit 13), there was a small difference in the change in retinal sensitivity from baseline between study eyes (all points: $+0.6 \pm 0.6$, leakage points: $+1.1 \pm 1.4$) and fellow eyes (all points: -0.3 ± 0.4 , leakage points: -0.8 ± 0.8) both when considering all points ($p=0.009$) and points in the area of leakage ($p=0.007$), favoring study eyes.

Effect of Intravitreal Ranibizumab on Area of Pigment Clumping

IMT2 is also characterized by pigment clumping and migration into the inner retina. The effect of intravitreal ranibizumab on the total retinal area involved with pigment clumping was investigated in this study. Both study and fellow eyes exhibited a monotonic increase in the area of pigment clumping, and no significant difference in the change from baseline was noted between them (data not shown).

DISCUSSION

Interventional studies for IMT2 are complicated by an incomplete understanding of its pathogenesis. The abnormal vascular permeability of telangiectatic vessels and the development of exudative neovascular disease in the subretinal space (and its response to anti-angiogenic therapy) suggested a dysregulation of pro-angiogenic factors within the retina.^{2, 15, 17, 18, 22, 25} While elevated intraocular VEGF levels have been demonstrated in other telangiectatic retinal diseases such as Coats' disease³², increased VEGF levels in IMT2 have not been directly measured. However, the marked reduction in vascular leakage in eyes treated with VEGF inhibition in previous case reports signal that elevated VEGF levels are likely present and contribute to aspects of disease pathology.^{12-14, 16, 17, 19-21, 23, 24, 33} Although IMT2 in its later stages involves significant central retinal atrophy and thinning, the effect of decreasing OCT retinal thicknesses with anti-VEGF treatment in the present study and others indicate the contribution of increased vascular permeability to a superimposed edematous process in the neuroretina.

Previous case series reporting the retrospective analysis of the treatment of non-neovascular IMT2 with anti-VEGF agents bevacizumab^{12-14, 16, 17, 19, 20} and ranibizumab^{21, 24, 33} have described mixed findings of clinical benefit with anti-VEGF treatment in patients with IMT2. Although the most significant functional improvements were described in patients with sub-retinal neovascularization^{15-18, 22, 23, 25}, other studies^{12, 20} have previously described a modest benefit in non-proliferative disease as well. Conversely, two additional studies^{14, 19} have reported no significant functional improvement after anti-VEGF treatment despite apparent anatomical changes in the decreased late-phase FA leakage and decreased central retinal thickness on OCT.

In the current study, the prospective, unilateral treatment study design with sustained VEGF inhibition with monthly ranibizumab over a course of 12 months has enabled us to systematically evaluate and correlate the anatomical and functional consequences of this therapeutic approach. Since the completion of the present study, a contemporaneous study with a similar study design has been recently published.²¹ In our study, as well as in this other prospective study, marked functional benefits resulting from intravitreal ranibizumab

were not observed, despite significant anatomical effects of decreased vascular permeability and reduced retinal edema. We did not detect any significant differences between study and fellow eyes in terms of mean changes in visual acuity, and while the comparison of changes in mean retinal sensitivities as measured by microperimetry suggested a possible trend favoring the study eye, these differences were small ($<2\text{dB}$) and do not probably on their own represent a pronounced and significant functional benefit that recommends the treatment.

As found in previous studies of anti-VEGF treatment in IMT2, we noted that when study treatment following monthly treatments over 12 months was stopped, a partial rebound increase in fluorescein leakage was noted 8 weeks later. With prolonged treatment cessation, it is possible that fluorescein leakage and measurements of OCT thickness would return to baseline levels. The question of whether potentially longer periods (>1 year) of anti-VEGF treatment can result in a durable absence of fluorescein leakage and reduced retinal edema after cessation of treatment will require studies of longer duration and follow up periods than the current one.

The induction of significant anatomical change but which produces only minimal functional improvement as a result of anti-VEGF treatment highlights an interesting discrepancy. One possibility for this difference may be due to the pre-existing central retinal atrophy in study eyes that was not ameliorated by the study treatment.⁸ As a result, while macular thickness may be correlated with retinal sensitivity in other retinal diseases such as diabetic macular edema³⁴, the presence of outer retinal atrophy in IMT2 may minimize potential sensitivity gains when retinal edema is reduced with anti-VEGF treatment. In addition, there is a converse hypothesis that sustained VEGF inhibition can actually accelerate retinal degeneration^{21, 35}, but how it applies in IMT2 is unclear. We did not detect any definite anatomical or functional signs of accelerated degeneration in treated study eyes over the 12-month duration of this study.

While it is known that the natural history of the IMT2 is characterized by slow progression in perifoveal telangiectasis and central retinal atrophy, as well as gradual decreases in visual acuity^{5, 8–10, 26–31}, interval changes were not clearly detected in untreated fellow eyes over the relatively short 12-month duration of the study. As a result, the hypothesis that sustained anti-VEGF treatment ameliorates the natural history of the disease can only be addressed in a study of longer duration. Nevertheless, it is interesting to note that mean retinal sensitivities in the fellow eye as measured by MP1 microperimetry, particularly in the area of late-phase FA leakage, did demonstrate a slight downward trend over the course of the study. This was observed in participants #1 through #4 (excluding participant #5 who underwent elective cataract extraction in the fellow eye), suggesting that microperimetry measurements of retinal sensitivity may be potentially helpful in detecting early stage disease progression in future investigations.

There are several aspects of the present study that may have limited the generalizability of its results, which include: the small number of participants enrolled, the relatively short duration of treatment, and the non-random assignment of the study eye. One assumption made in the comparison of study to fellow eyes relates to the concordance of disease

progression between the two eyes of each patient with IMT2. Although clinically characterized as a bilateral disease, population-based studies have differed on the degree of agreement in clinical findings between fellow eyes of individual patients.^{3,4} In our cohort, baseline measurements showed varying interclass correlation between eyes: BCVA ($\rho = -0.13$), central OCT thickness ($\rho = 0.50$), and area of late-phase FA leakage ($\rho = 0.91$). Although the high level of interclass correlation between study and fellow eyes when measuring baseline late-phase FA leakage, one of the phenotypic hallmarks of IMT2, does lend some validity to the present study design, it does not alone guarantee uniform disease progression between study and fellow eyes. Also, considerations used in the choice of the study eye can potentially also introduce bias in the comparisons of visual acuity made between the study eye and the fellow eye. However, this is unlikely to have contributed significantly, as the visual acuity of all eyes in the study remained relatively stable throughout the duration of the study (with 9 out of 10 eyes demonstrating a change in visual acuity of ≥ 10 letters at final visit), despite the variation in visual acuity at baseline.

In conclusion, we report that monthly treatment with ranibizumab up to one year in IMT2 was associated with minimal adverse events and no detectable acceleration of disease progression in study participants. Although improvements in some anatomical features of IMT2 were observed with treatment, a broad and significant positive functional effect of ranibizumab was also not detected over continuous inhibition over a 12-month duration. While microperimetric measurements suggest the possibility of increased retinal sensitivity in areas of decreased retinal edema, these observations require further confirmation in larger studies. Future studies may examine the impact of VEGF inhibition in earlier stages of the disease when retinal atrophy is less advanced but vascular leakage is already present. For affected patients in general, our results indicate that anti-VEGF therapy over this time frame did not provide a general and prominent benefit.

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Summary statement

The current phase II clinical study employed a paired, unilateral treated-eye design to assess sustained 12-month intravitreal ranibizumab on anatomical and functional progression in patients with IMT2. The study results suggest that ranibizumab has no treatment impact on visual acuity, despite decreasing vascular leakage and retinal edema.

Figure 1. Effect of intravitreal ranibizumab on visual acuity in participants with IMT2
(A) Summary of visual acuity change from baseline at all study visits for each study participant. Each histogram column shows the change in visual acuity score (in ETDRS letters) from baseline for all study visits (visits 1 through 14) arranged in order. Changes for the study eye (*top*) and untreated fellow eye (*bottom*) are shown. **(B)** Mean change in visual acuity score from baseline over time for study eyes (n=5) and fellow eyes (n=5). The error bars represent standard deviation. No statistical difference was observed between study eyes and fellow eyes at any time point ($p>0.05$ for all comparisons, paired t-test).

Figure 2. Effect of intravitreal ranibizumab on late-phase leakage on fluorescein angiography (FA) in participants with IMT2

(A) Summary of change in the area of late-phase leakage on FA from baseline for each study participant. Each histogram column shows the percent change in the area of late-phase leakage compared to baseline for the treated study eye (*top*) and untreated fellow eye (*bottom*). The response to treatment in all five study eyes was characterized by a prominent decrease in the area of late leakage. Changes from baseline were variable during study follow-up in three out of five fellow eyes (participants #1, #2, and #3) and increased in two out of five fellow eyes (participants #4 and #5). Prior to visit 8 (*arrow*), participant #5 underwent cataract extraction and intraocular lens implantation in the fellow eye, which demonstrated a post-procedural increase in late-phase leakage that is likely attributable to the effects of surgery (Irvine-Gass syndrome). (B) Mean change in late-phase leakage area from baseline over time, excluding data from participant #5 ($n=4$, for study and fellow eyes). Significant differences in mean change between study and fellow eyes were apparent following one ranibizumab treatment ($p=0.03$, paired t-test) and increased to a maximum after four to five treatments. The error bars represent standard deviation.

Figure 3. Clinical effect of intravitreal ranibizumab on vascular leakage and retinal thickness in patients with IMT2

(A) Late-phase phase fluorescein angiographs of participant #2 at baseline (*left*) and visit #2 (*right*) in the study (*top*) and fellow eye (*bottom*). Eight weeks following the baseline visit and two consecutive intravitreal injections of ranibizumab, the study eye demonstrated a marked reduction in the area of late-phase FA leakage, while the untreated fellow eye showed little interval change. (B) Corresponding optical coherence tomography (OCT) horizontal B-scans traversing the center of the fovea. In the study eye (*top*), the fovea (*arrow*) demonstrated reduction in central retinal thickness with a decrease in the size of hyporeflective intraretinal cavities. In the untreated fellow eye (*bottom*), central retinal thickness remained relatively stable.

Figure 4. Effect of intravitreal ranibizumab on retinal thickness as measured by optical coherence tomography (OCT) in participants with IMT2

(A) Summary of change in the central subfield retinal thickness on OCT from baseline for each study participant. Each histogram column shows the percent change from baseline in retinal thickness measured in the central (1mm diameter) subfield in the treated study eye (*top*) and untreated fellow eye (*bottom*). The response to treatment in all five study eyes was characterized by a predominant decrease in central subfield thickness. In fellow eyes, changes from baseline were smaller and more variable in four out of five fellow eyes (participants #1, #2, #3, and #4). Participant #5 underwent cataract extraction in the fellow eye prior to visit 8 (*arrow*), which demonstrated a post-procedural increase in OCT thickness that is likely attributable to the effects of surgery (Irvine-Gass syndrome). (B) Mean change in central subfield retinal thickness from baseline over time, excluding data from participant #5 ($n=4$, for study and fellow eyes). Significant differences in mean change between study and fellow eyes were apparent following one ranibizumab treatment ($p=0.03$, paired t-test) and maintained thereafter. (C–F) Similar trends in retinal thickness were also observed in all four paracentral quadrants adjoining the central retinal subfield. Mean decreases in retinal thickness in treated eyes were greatest in the temporal paracentral quadrant compared to the other (nasal, superior, and inferior) paracentral quadrants. The

error bars represent standard error of the mean. Asterisks indicate significant differences between study and fellow eyes (paired t-test, $n=4$).

Figure 5. Effect of intravitreal ranibizumab on retinal sensitivity as measured by microperimetry in participants with IMT2

Microperimetric measurements were performed using the Nidek MP-1 microperimeter. A 68-loci circular grid centered on the macula and covering the central 20° was employed. **(A)** The ability of the participant to respond to stimulus light projected at particular retinal loci was evaluated, and retinal sensitivity at each loci was measured on a scale from 0 (low sensitivity) to 20 dB (high sensitivity). **(B)** A subset of testing points was also identified as being located within the retinal area involving late-phase fluorescein leakage by overlaying the MP1 test grid upon a late-phase image of the fluorescein angiograph (*left*). In this way, two sets of points were identified for analysis: (1) all 68 points in the testing grid, and (2) a subset of points in the testing grid found within the area of the retina involving late-phase FA leakage (points highlighted in red, *right*). Summaries of the mean change in retinal sensitivity from baseline at visits 3, 9, and 13 are shown for each study patient for **(D)** all points and **(E)** points in the area of leakage only. Each histogram column shows the mean change in retinal sensitivity compared to baseline visit for the treated study eye (*top*) and untreated fellow eye (*bottom*). By the end of follow-up, three study eyes exhibited a net increase in retinal sensitivity (participants #2, #3, and #4), compared to none of the fellow eyes. Participant #5 underwent cataract extraction in the fellow eye prior to visit 8 (arrow). **(F–G)** Mean change in mean retinal sensitivity from baseline was calculated for all testing

points (**F**) and for points involving FA leakage only (**G**), excluding data from participant #5 (n=4, for study and fellow eyes).

Table 1

Baseline Characteristics of Study Participants

Patient	Sex	Age	Race	Study Eye	VA Study Eye (ETDRS letters, Snellen equivalent)	VA Fellow Eye (ETDRS letters, Snellen equivalent)	OCT Thickness, Central Study Eye (μm)	OCT Thickness, Central Fellow Eye (μm)	FA Leakage, Late Study Eye (mm^2)	FA Leakage, Late Fellow Eye (mm^2)
1	F	64	Black	OS	61, 20/63	49, 20/100	198	282	4.53	4.93
2	M	70	Asian	OD	54, 20/80	58, 20/80	189	197	4.37	4.70
3	M	62	White	OD	82, 20/25	57, 20/80	239	236	0.34	0.59
4	M	68	Hispanic	OD	48, 20/125	69, 20/40	150	164	0.99	1.01
5	F	63	Hispanic	OD	69, 20/40	74, 20/32	244	217	2.35	0.48
Mean		65.3			62.8, 20/63	61.4, 20/63	204	219	2.5	2.3
SD		3.3			13.3	10	38	44	1.9	2.3

* Abbreviations: VA = visual acuity, ETDRS = Early Treatment of Diabetic Retinopathy Study, OCT = optical coherence tomography, FA = fluorescein angiogram, μm = microns, mm^2 = square millimeters