Progression of Lesion Size in Untreated Eyes With Exudative Age-Related Macular Degeneration

A Meta-analysis Using Lineweaver-Burk Plots

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Objective: To test the hypothesis that the natural history of choroidal neovascularization lesion size is uniform across prior randomized controlled clinical trials of exudative age-related macular degeneration (AMD), with apparent differences arising from different entry times of eyes into clinical trials.

Methods: We conducted a retrospective meta-analysis of control eye data from 5 age-related macular degeneration trials (Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; Verteporfin in Photodynamic Therapy; VEGF Inhibition Study in Ocular Neovascularization; Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; and Phase 3b, Multicenter, Randomized, Double-masked, Sham Injection-controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic Choroidal Neovascularization Secondary to AMD Study), which were plotted on a double reciprocal plot of 1/lesion size (disc area) vs 1/time (months after enrollment). To account for the different entry times, we introduced a horizontal translation factor to shift each data subset until $r^2$ was maximized for the cumulative trend line.

Results: Cumulative data for untreated control eyes fit a straight line on a double reciprocal plot ($r^2=0.98$) after the introduction of horizontal translation factors. Our model predicts that a choroidal neovascular lesion will eventually enlarge to a size of 10.6 disc areas without treatment and that the lesion will reach half of its maximum size within 14.0 months after onset of exudation. The linear expansion rate of untreated lesions is approximately 26.0 $\mu$m per day for the smallest lesions and decreases gradually as the lesions enlarge.

Conclusions: The pattern of choroidal neovascularization lesion size enlargement in AMD eyes is uniform across a wide range of clinical trials, with apparent differences arising from different entry times of patients into various trials. The main determinant of choroidal neovascularization lesion size enlargement is the duration of exudative disease.


AGE-RELATED MACULAR DEGENERATION (AMD) is the leading cause of irreversible blindness in people older than age 50 years in the developed world. The wet, or exudative, form of this disease is characterized by the growth of abnormal choroidal vessels within the Bruch’s membrane into the space between the Bruch’s membrane and the retinal pigment epithelium or between the retinal pigment epithelium and the overlying neural retina. Some cases of exudative AMD arise from the growth of angiomatosus vessels within the neural retina. Although exudative AMD represents only 10% to 15% of the overall prevalence of AMD, it is responsible for more than 80% of cases of severe visual loss.

The current standard of care for treating exudative AMD is repeated intravitreal injections of bevacizumab and ranibizumab (Genentech), which are monoclonal antibodies to vascular endothelial growth factor (VEGF), or repeated intravitreal injections of aflibercept (Regeneron), which is a fusion protein that binds VEGF and placental growth factor. During the past 2 decades, a number of clinical trials have been performed to investigate other modalities, including thermal laser photocoagulation, surgical excision of the neovascular tissue, photodynamic therapy with verteporfin, and pharmacological therapy with anecortave acetate and pegaptanib. Although most of these modalities are used infrequently or have been abandoned, the data from these studies provide significant and important information on the natural history of untreated eyes.
eyes. For example, we have noted previously that there are significant differences in the initial visual acuity among untreated control eyes in patients who entered clinical trials during this 2-decade window (eg, the Macular Photocoagulation Study and Treatment of Age-Related Macular Degeneration with Photodynamic Therapy). Using data from these trials and others, we have shown that apparent differences in the initial visual acuity in these untreated control eyes arise from different entry times of these eyes into clinical trials. In addition, we were able to use double reciprocal (Lineweaver-Burk) plots to model visual acuity as a function of time of untreated exudative AMD eyes.17

As an extension of our prior work, because choroidal neovascularization lesion size and visual acuity are highly correlated,18-20 we sought to determine whether lesion size as a function of time was also linear on a double reciprocal plot. We used this model to draw inferences on the progression of lesion size as a function of time in untreated exudative AMD eyes.

Data for modeling the natural progression of lesion size as a function of time were obtained from the following studies: Treatment of Age-Related Macular Degeneration with Photodynamic Therapy21, Verteporfin in Photodynamic Therapy22, VEGF Inhibition Study in Ocular Neovascularization23; Minimally Classic/Occlult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration24; and Phase 3b, Multicenter, Randomized, Double-masked, Sham Injection-controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic Choroidal Neovascularization Secondary to AMD25; TAP, Treatment of Age-Related Macular Degeneration With Photodynamic Therapy; VISION 1, Study 1003 within the VEGF Inhibition Study in Ocular Neovascularization; VISION 2, Study 1004 within the VEGF Inhibition Study in Ocular Neovascularization.

Figure 1 shows choroidal neovascularization lesion size as a function of time in the untreated control eyes of all studies. The lesion size increases as a function of time in all studies (Figure 1), which is not surprising because there is progressive enlargement of lesions and deterioration of visual function in eyes with exudative AMD without treatment. The asymptotic increase in lesion size suggests that there is little further anatomic enlargement of lesions once they have reached a certain size. We have shown previously that visual acuity as a function of time for untreated exudative AMD eyes exhibits similar asymptotic behavior.17 Such asymptotic behavior exhibits linearity on double reciprocal (Lineweaver-Burk) plots. As an extension of our previous work, we used a similar model to analyze the progression of lesion size over time using double reciprocal plots.

A double reciprocal plot of 1/lesion size (disc areas) vs 1/time (months after enrollment) is shown in Figure 2. Best-fit lines suggest that 1/lesion size (disc areas) vs 1/time (months after enrollment) was linear for each individual data set, reinforcing the concept that each data set exhibits a similar pattern of lesion size enlargement over time. Following methods we used to model the behavior of visual acuity over time, we corrected for differences in entry time into clinical trials by adding a horizontal translation factor (expressed in months) to each data set; essentially, this changed the horizontal axis from...
1/time (months after enrollment) to 1/time (months of exudative disease), where months of exudative disease = (months after enrollment) + (horizontal translation factor expressed in months) (compare Figure 2 and Figure 3). To determine the optimum horizontal translation factor for each data set in Figure 2, we used previously published translation factors\(^2\) as starting points and then adjusted the translation factor for each clinical trial in an iterative fashion until we maximized the correlation coefficient \(r^2\) for the overall trend line shown in Figure 3. The horizontal translation factor (expressed in months) for each trial necessary to achieve the highest value of \(r^2\) are shown in the Table.

The optimum linear fit achieved on a double reciprocal plot of the untreated control eye data shown in Figure 3; the equation describing this line is 1/lesion size (disc areas) = 1.3248/time (months of exudative disease) + 0.0942 (ie, equation 1). The high value of \(r^2\) (0.98) suggests that the main factor determining the progression of lesion size as a function of time is the duration of exudative disease. Some physical insight into eyes with exudative AMD can be gained from careful examination of this equation. For example, as time approaches infinity, 1/time (months of exudative disease) approaches 0 and equation 1 simplifies to 1/lesion size (disc areas) = 0.0942 (ie, equation 2) or lesion size (disc areas) = (1/0.0942) = 10.6 (ie, equation 3). This implies that the end-stage choroidal neovascularization lesion size in untreated eyes is approximately 10.6 disc areas. Also, from equation 1 and equation 3, the number of months that disease must progress before lesions reach half their maximum size is 14.0 months.

The straight line in Figure 3 can be used to generate a smooth curve of lesion size (disc areas) vs time (months of exudative disease) (Figure 4). This graph demonstrates the asymptotic behavior of choroidal neovascularization lesion size as a function of time; for clarity, we explicitly drew the asymptote at a value of lesion size = 10.6 disc areas. Converting the linear equation (equation 1) in Figure 3 to its equivalent curve-linear form, we arrived at: 

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\text{Figure 2. Lineeweaver-Burk plot of choroidal neovascularization lesion size as a function of time after enrollment of patients into prior clinical trials for treatment of exudative age-related macular degeneration. The data points are shown on a double reciprocal plot of 1/lesion size (disc areas) vs 1/time (months after enrollment). To generate this figure, data from Figure 1 is used to plot 1/lesion size (disc areas) along the vertical axis and 1/time (months after enrollment) along the horizontal axis. This yields a series of lines for the behavior of average lesion size in untreated control eyes. Note that individual lines are not aligned with one another and appear to have different slopes.}

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\text{MARINA indicates Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; PIER, Phase 3b, Multicenter, Randomized, Double-masked, Sham Injection-controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic Choroidal Neovascularization Secondary to AMD; TAP, Treatment of Age-Related Macular Degeneration With Photodynamic Therapy; VIP, Verteporfin in Photodynamic Therapy; VISION 1, Study 1003 within the VEGF Inhibition Study in Ocular Neovascularization; VISION 2, Study 1004 within the VEGF Inhibition Study in Ocular Neovascularization.}

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\text{Table. Horizontal Translation Factors for Clinical Trials for the Treatment of Exudative Age-Related Macular Degeneration}

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<td>VIP</td>
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<td>VISION 1</td>
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<td>VISION 2</td>
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Abbreviations: MARINA, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; PIER, Phase 3b, Multicenter, Randomized, Double-masked, Sham Injection-controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic Choroidal Neovascularization Secondary to AMD; TAP, Treatment of Age-Related Macular Degeneration With Photodynamic Therapy; VIP, Verteporfin in Photodynamic Therapy; VISION 1, Study 1003 within the VEGF Inhibition Study in Ocular Neovascularization; VISION 2, Study 1004 within the VEGF Inhibition Study in Ocular Neovascularization.
the best-fit line shown in Figure 4: lesion size (disc areas) = (10.6 × time [months of exudative disease])/ (14.0 + time [months of exudative disease]) (ie, equation 4). In Figure 4, the arrows also mark the control eyes’ entry times into each of the aforementioned clinical trials.

Our data can be used to estimate the growth rate of untreated neovascular lesions as a function of time and lesion size (Figure 5). The growth rate in disc areas per month (Figure 3A) can be obtained by taking the first derivative of the best-fit line shown in Figure 4. To generate the graph in Figure 5B, we then changed the y-axis of the graph in Figure 3A from change in lesion size (disc areas/month) to lesion radius growth rate (micrometers/day), with the assumption that the lesions are round and that 1 disc area = 2.54 mm$^2$. The linear growth rate, in micrometers per day, varied with the duration of exudative disease (Figure 5B). We estimated that the growth rate at month 36 of exudative disease would be 7.3 μm per day. To determine the linear growth rate as a function of lesion size (Figure 5C), we changed the x-axis of Figure 5B from time (months of exudative disease) to lesion size (disc areas). This shows that the linear growth rate was highest for the smallest lesions. By extrapolation, we estimated that the linear growth rate was 26.0 μm per day for the smallest lesions, and it gradually decreased to 6.3 μm per day when lesions enlarged to 8 disc areas.

Numerous studies have shown that visual acuity and choroidal neovascularization lesion size are highly correlated in exudative AMD. Building on our previous study, we used similar methods to model lesion size en-

**Figure 4.** Choroidal neovascularization lesion size as a function of the duration of exudative disease. This curve is generated directly from Figure 3. Lesion size approaches an asymptotic value of 10.6 disc areas. Arrows show entry points of patients into individual clinical trials. MARINA indicates Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; PIER, Phase 3b, Multicenter, Randomized, Double-masked, Sham Injection–controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic Choroidal Neovascularization Secondary to AMD; TAP, Treatment of Age-Related Macular Degeneration With Photodynamic Therapy; VIP, Verteporfin in Photodynamic Therapy; VISION 1, Study 1003 within the VEGF Inhibition Study in Ocular Neovascularization; VISION 2, Study 1004 within the VEGF Inhibition Study in Ocular Neovascularization.

**Figure 5.** Growth rate of choroidal neovascular lesions. A, The curve shows the change in lesion size as a function of time and is generated by taking the first derivative of the best-fit line for the data in Figure 4. B, The curve shows the linear expansion rate at the border of neovascular lesions as a function of time. It is generated from the curve in part A, assuming that lesions are circular and that 1 disc area = 2.54 mm$^2$. It predicts that the linear expansion rate varies with the duration of disease. C, The curve shows the linear expansion rate as a function of lesion size. It is generated from the curve in part B by changing the x-axis. Note that the leading edge grows fastest for the smallest lesions (26.0 μm/day) and the growth rate decreases as the lesions enlarge.

**COMMENT**

Several insights can be gained from the data. First, the high correlation ($r^2 = 0.98$) for the cumulative best-fit line in Figure 3 suggests that the main determinant of lesion size progression is the duration of exudative disease. The data suggest that the apparent differences in the initial and final choroidal neovascularization lesion sizes in the different trials result from different entry times of eyes into the trials. Second, the raw data were drawn from a wide range of trials, including lesions that were classified as predominantly classic, minimally classic, and occult with no...
classic on fluorescein angiography. This indicates that the natural history of choroidal neovascular lesion enlargement exhibits similarities across all 3 fluorescein angiographic subtypes. Third, the vertical intercept of Figure 3 suggests that the final lesion size for untreated exudative AMD eyes is 10.6 disc areas, which is consistent with clinical observations that choroidal neovascular membranes reach a maximum size of about 12 disc areas in most patients, unless extra macular bleeding and fibrosis develop from multiple ingrowth sites. Fourth, we were able to estimate the enlargement rate of choroidal neovascular lesions from Figure 3. Figure 5 predicts that the longer the duration of exudative disease, the slower the rate of choroidal neovascular lesion enlargement. By extrapolation, for the smallest lesions, the edge of choroidal neovascular membranes advances at 26.0 μm per day. This implies that at the onset of choroidal neovascularization, de novo lesions can expand rapidly; our data predict that these lesions can go from being undetectable to having a diameter of 416 μm by 8 days after development. These numbers are consistent with the clinical observation that patients can rapidly develop small neovascular lesions in areas that appeared normal days to weeks earlier on clinical examination. We predict that the edge of choroidal neovascular membranes will advance at 7.3 μm per day at month 36 of exudative disease. These numbers are consistent with previously published results. Klein et al. reported that the growth rate of choroidal neovascular membranes ranged from 1 to 24 μm per day, with an average of 10 μm per day. Vander et al. reported that the growth rate of sub-retinal neovascularization in any one direction ranged from 0 to 37 μm per day, with an average of 9 μm per day.

Our study suggests that even the earliest enrolled patients have had exudative AMD for 7.7 months before their entry into clinical trials based on their initial choroidal neovascularization lesion size, suggesting either a delay in enrollment or a period of subclinical neovascularization. The concept of subclinical choroidal neovascularization is supported by both our natural history studies of exudative AMD based on visual acuity and by numerous histopathologic studies of AMD eyes. For example, Sarks demonstrated the presence of choroidal neovascularization in 20% of the 150 eyes examined histopathologically, suggesting that subclinical choroidal neovascularization may be much more common than the development of symptomatic exudation because the prevalence of exudative AMD in the United States is less than 1.5% in people older than 40 years of age. In another histopathologic study involving 760 eyes, Green and Enger reported the presence of choroidal neovascularization in 38.2% of the eyes, but the neovascularization invaded the subretinal space in only 5 eyes. We have previously shown that it takes 10.88 months for visual acuity to deteriorate halfway to its final score in patients with active exudative AMD. From equation 1 and equation 3, we calculate that it takes 14.0 months of exudative disease for choroidal neovascular lesions to reach half their maximum size. Thus, by 10.88 months after the onset of exudation, patients have lost half their vision but the lesion is less than half of its maximal size, measured in disc areas. It is not surprising that visual acuity deteriorates at a rate faster than the increase in lesion size because it is known that a choroidal neovascular lesion can adversely affect an area of retina that is larger than the lesion itself owing to adjacent accumulation of subretinal fluid, intraretinal fluid, hemorrhage, and/or pigment epithelial detachment. Prior studies measuring the size of lesions that have been surgically removed prior to the advent of anti-VEGF therapy have also demonstrated that lesion size determined histologically was often larger than the size determined on fluorescein angiography.

In summary, we have used a meta-analysis of prior clinical trials to demonstrate that choroidal neovascularization lesion size data from untreated exudative AMD eyes can be fit along a straight line on a double reciprocal plot with a high level of correlation ($r^2 = 0.98$). An important implication of this meta-analysis is that the main determinant of choroidal neovascularization lesion size enlargement is the duration of exudative disease and that the linear expansion of small lesions occurs at a higher rate than large lesions.

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REFERENCES


