JOURNAL CLUB

Estimated Cases of Legal Blindness and Visual Impairment Avoided Using Ranibizumab for Choroidal Neovascularization

Non-Hispanic White Population in the United States With Age-Related Macular Degeneration

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Objective: To estimate the number of non-Hispanic white individuals in the United States avoiding legal blindness and visual impairment from neovascular age-related macular degeneration (AMD) with ranibizumab availability.

Methods: Modeling of visual acuity outcomes from phase 3 ranibizumab trials to incidence rates of neovascular AMD from population-based studies.

Results: If no treatment were given, of the 103 582 individuals developing neovascular AMD for which ranibizumab would be indicated and available, 16 268 would become legally blind in 2 years. Monthly ranibizumab would reduce the incidence of legal blindness in 2 years by 72% (95% confidence interval [CI], 70% to 74%) to 4484 individuals. If no treatment were given, 34 702 would become visually impaired. Monthly ranibizumab would reduce the incidence of visual impairment in 2 years by 37% (95% CI, 35% to 39%) to 21 919 cases.

Conclusions: Ranibizumab should have a substantial effect on reducing the magnitude of legal blindness and visual impairment within 2 years after diagnosis of neovascular AMD among non-Hispanic white individuals in the United States. Although racial subgroups other than non-Hispanic whites were not considered (because there is limited information in the literature regarding incidence rates of choroidal neovascularization in other populations) and although these results assume access to and application of monthly ranibizumab for 2 years, the number of individuals developing legal blindness or vision impairment from neovascular AMD should be reduced dramatically if monthly ranibizumab is applied when indicated.

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BEFORE RANIBIZUMAB BECAME available in 2006, neovascular age-related macular degeneration (AMD) was reported to be the leading cause of blindness in individuals 50 years or older in the United States and throughout many parts of the world.[1] Researchers estimate that without the introduction of new therapies, by 2050 there will be 1.6 million cases of blindness and visual impairment due to neovascular AMD.[2] Although photodynamic therapy (PDT) with verteporfin (Visudyne; QLT Inc, Vancouver, British Columbia, Canada)[3] as well as intravitreal pegaptanib sodium (Macugen; Eyetech Pharmaceuticals, Cedar Knolls, New Jersey)[4] reduces the risk of vision loss compared with no treatment for choroidal neovascularization (CNV) in AMD, most treated cases still have substantial vision loss resulting in legal blindness when both eyes have best-corrected visual acuity of 20/200 or worse.

Subsequent reports[5,6] show that monthly intravitreal ranibizumab (Lucentis; Genentech, Inc, South San Francisco, California) injections for 2 years in eyes with CNV from AMD not only reduce the risk of substantial vision loss but also increase the chance of substantial vision gain. A reduced fixed-dosing interval also reduces the risk of vision loss[7] but has not been shown to increase the chance of vision gain. Given these recent findings and the magnitude of legal blindness from neovascular AMD, this study was undertaken to estimate the number of individuals in the United States who might avoid legal blindness or visual impairment (when both eyes have best-corrected visual acuity of ≤20/40) from neovascular AMD with use of ranibizumab.

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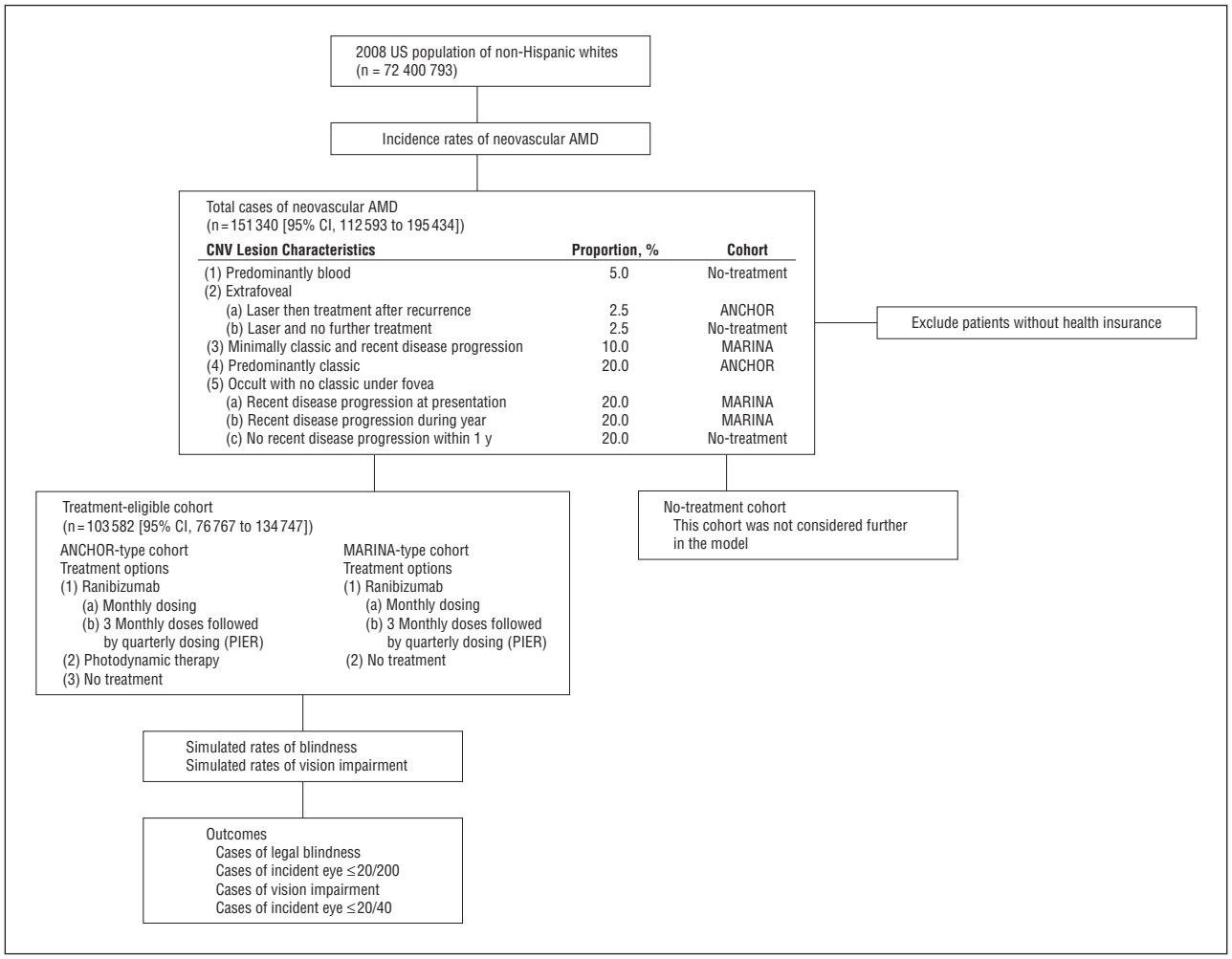

Figure. Model schematic. Incident cases of neovascular age-related macular degeneration (AMD) were derived by multiplying the number of individuals in each age and gender stratum[8] by the age- and gender-specific incidence rates of neovascular AMD obtained from the Beaver Dam Eye Study[9] estimated 15-year cumulative incidence of AMD assuming that events occurred evenly during the observation period. Incident cases of neovascular AMD from 1 year were followed up in the model for 2 years. Among individuals with AMD in 1 eye, 33% were estimated to have choroidal neovascularization in the fellow eye at baseline based on information from the Age-Related Eye Disease Study (AREDS) report No. 11[10], the Anti-Vascular Endothelial Growth Factor (VEGF) Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR)[5], and the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA)[6] studies. CI indicates confidence interval; CNV, choroidal neovascularization; and PIER, Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab.

METHODS

A schematic of the model used in this study is illustrated in the **Figure**. The number of non-Hispanic whites 50 years or older in the United States in 2008 was estimated from US Census Bureau data.[8] Incident cases of neovascular AMD were derived by multiplying the number of individuals by the incidence rate of neovascular AMD in each age and gender stratum obtained from the Beaver Dam Eye Study[9] estimated 15-year cumulative incidence of AMD, assuming that events occurred evenly during the observation period. Incident cases of neovascular AMD from 2008 were followed up in the model for 2 years. Among individuals with AMD in 1 eye, 33% were estimated to have CNV in the fellow eye at baseline based on information from phase 3 ranibizumab trials: the Age-Related Eye Disease Study (AREDS) report No. 11[10] and the Anti-Vascular Endothelial Growth Factor (VEGF) Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR)[5] and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA)[6] studies.

Incident cases of neovascular AMD were classified further according to lesion characteristics (Figure). Five percent of incident cases were assumed to be predominantly blood, for which no treatment presumably is indicated. Five percent of cases were classified as having extrafoveal lesions. Half of these cases (2.5%) presumably would receive laser treatment with no recurrent CNV, and the remaining half (2.5%) were assumed to have recurrent CNV with a predominantly classic pattern for which ranibizumab would be indicated, with visual acuity outcomes based on the ANCHOR study.[5] Ten percent were assumed to have minimally classic lesions and recent disease progression for which ranibizumab would be indicated, with visual acuity outcomes based on the MARINA study.[6] An additional 20% of cases were presumed to be predominantly classic lesions for which ranibizumab would be indicated, with visual acuity outcomes based on the ANCHOR study. The remaining 60% of cases were classified as lesions extending under the center of the macula with a fluorescein angiographic pattern of occult with no classic CNV and were further stratified as 20% having recent disease progression at presentation (when ranibizumab would be indicated for occult with no classic CNV lesions), with

visual acuity outcomes based on the MARINA study; 20% having recent disease progression during the year (when ranibizumab would be indicated), with visual acuity outcomes based on the MARINA study; and 20% having no recent disease progression in 1 year (when ranibizumab would not necessarily be indicated). The distribution of these lesions among incident CNV cases was tested in a sensitivity analysis in which these presumptions were doubled or halved individually.

Thus, lesions were classified into 3 cohorts (Figure) according to what treatments likely would be provided. The no-treatment cohort consisted of lesion types for which further treatment was not indicated; therefore, this cohort was excluded from the analysis. The ANCHOR-type cohort included lesions that could be treated with outcomes assumed to be similar to those in the ANCHOR study.[5] The MARINA-type cohort included lesions that could be treated with outcomes assumed to be similar to those in the MARINA study.[6] The model assumed that individuals without health insurance would not receive treatment of any kind, including 14.2% of individuals 45 to 64 years of age[11] and 1.5% of individuals 65 years or older.[11] No other factors that excluded treatment for CNV were considered.

The 2-year rates of blindness and visual impairment were estimated using Markov modeling[12-15] (@Risk for Excel, version 5.5.1; Palisade Corporation, Ithaca, New York, and TreeAge Pro 2009 Suite; TreeAge Software, Inc, Williamstown, Massachusetts), with monthly cycles that accounted for the competing risks of blindness and mortality. The model used 2-dimensional Monte Carlo simulation to account for patient variability and parameter uncertainty. To achieve stable rates, 300 replications of a simulated 10 000-patient cohort were conducted. For each simulated patient, the visual acuity of each eye was assigned at baseline using data from a specific patient from ANCHOR[5] or MARINA[6] as described in the preceding paragraphs. The letter score change in 2 years was sampled from the same patient to preserve the correlation between baseline visual acuity and visual acuity change at 2 years. A subgroup analysis of the ANCHOR data conducted by Kaiser and colleagues[16] suggested that the amount of visual acuity change is likely to be conditional on the patient's baseline visual acuity. Mortality risk was applied using US age- and gender-specific mortality rates for the non-black population. The simulation also accounted for patients' risk of treatment discontinuation each month. While the patient was not receiving treatment, the visual acuity change was assumed to decline by 1.6% per month based on the 2-year sham results in the MARINA study (−14.9 letters in 24 months).[6]

COMPARISON GROUPS

In the base case, 27.5% of the incident cases were classified as having CNV lesion characteristics that do not require treatment. An additional 22.5% of cases were classified in the ANCHOR-type cohort, for which ranibizumab was compared with outcomes using PDT with verteporfin and with no treatment. The remaining 50% of cases were classified as the MARINA-type cohort. In this group, ranibizumab was compared only with no treatment using the sham treatment group in the MARINA study.[6]

BASELINE VISUAL ACUITY AND VISUAL ACUITY CHANGE

The baseline visual acuity was based on the distributions of visual acuity in the treated eyes of patients in the respective ANCHOR[5] and MARINA[6] cohorts. These baseline distributions were assumed to be applicable to the entire cohort of incident neovascular AMD in the United States. In the fellow eye without CNV at baseline, the visual acuity among incident cases of AMD was estimated using the distribution of baseline visual acuity in the fellow eye of patients without CNV in the ANCHOR or MARINA study as appropriate. In the fellow eye with CNV at baseline, the visual acuity was estimated by using the distribution of baseline visual acuity in the fellow eye of patients with CNV in the ANCHOR or MARINA study.

Visual acuity change was modeled as the letter score change from baseline during a 2-year period observed in the ANCHOR and MARINA studies. Individual variation in the amount of visual acuity change was taken into account using sampling from the trial data. The visual acuity change from each study and each treatment was applied to the corresponding CNV lesion subtype and comparison group in the model, respectively. Only the efficacy from a 0.5-mg dose of ranibizumab was applied. In the fellow eye, the visual acuity was allowed to change according to the change observed in the ANCHOR and MARINA studies for patients with and without established CNV at baseline. If CNV developed in a fellow eye without CNV at baseline, the fellow eye received the same treatment as the first eye, and the estimated visual acuity letter score change was based on the MARINA study data. This assumes that most of these lesions are similar to those in the MARINA study.

MODEL OUTCOMES

The key outputs from the model were the number of cases of legal blindness and visual impairment. The difference between treatments yielded the total cases of blindness avoided. *Legal blindness* was defined as a letter score of 38 or lower (comparable to a Snellen equivalent of ≤20/200) in the better-seeing eye. *Monocular blindness* was defined as a letter score of 38 or lower in 1 eye. *Visual impairment* was defined as a letter score of 68 or lower (comparable to ≤20/40, which includes the patients already classified as having legal blindness) in the better-seeing eye. Visual impairment was tracked for each eye separately during the simulation.

SENSITIVITY ANALYSES

The base case analysis was carried out assuming that ranibizumab was given monthly based on the ANCHOR[5] and MARINA[6] study experience. A scenario analysis was performed to estimate the outcomes assuming that ranibizumab was given on a reduced, fixed-frequency dosing schedule[7] based on visual acuity outcomes of a regimen of monthly treatment for the first 3 months and then every 3 months thereafter. Separate scenario analyses also were performed to estimate the outcomes by doubling or halving the assumed proportion of CNV lesion characteristics on incident cases of legal blindness in 2 years.

Most of the key inputs into the model were evaluated using a probabilistic analytic framework whereby the parameter uncertainties were characterized by distributions (**Table 1**) and sampled during the Monte Carlo simulation. The results are reported as an interval around the mean estimate that captured 95% of all possible values for each outcome.

RESULTS

INCIDENCE OF CNV FROM AMD IN 2008

According to the age- and gender-specific rates from the Beaver Dam Eye Study[9] and the data from the US Census Bureau,[8] the model predicted that 151 340 (95% confidence interval [CI], 112 593 to 195 434) non-Hispanic

Table 1. Specification of the Model Parameter Values and Distributions Used for the Simulation

Parameter	Value	Distribution[a]	Source
Population size of non-Hispanic whites			
Women by age, y			
50 to 54	7 869 390	NA	US Census Bureau[8]
55 to 64	13 095 270	NA	US Census Bureau[8]
65 to 74	8 405 019	NA	US Census Bureau[8]
≥75	9 590 532	NA	US Census Bureau[8]
Men by age, y			
50 to 54	7 722 934	NA	US Census Bureau[8]
55 to 64	12 505 149	NA	US Census Bureau[8]
65 to 74	7 330 307	NA	US Census Bureau[8]
≥75	5 882 192	NA	US Census Bureau[8]
Incidence rates of neovascular AMD, mean (SE), by age, y			
50 to 54	0.0004 (0.0002)[b]	Gamma (alpha = 3.00, beta = 0.0001)	Estimated based on Beaver Dam Eye Study[9]
55 to 64	0.0018 (0.0005)[b]	Gamma (alpha = 13.00, beta = 0.0001)	Estimated based on Beaver Dam Eye Study[9]
65 to 74	0.0025 (0.0006)[b]	Gamma (alpha = 17.00, beta = 0.0001)	Estimated based on Beaver Dam Eye Study[9]
≥75, Women	0.0056 (0.0018)[b]	Gamma (alpha = 10.06, beta = 0.0006)	R.V. (personal communication, September 4, 2009)
≥75, Men	0.0014 (0.0010)[b]	Gamma (alpha = 2.00, beta = 0.0007)	R.V. (personal communication, September 4, 2009)
Patients with AMD who had CNV in fellow eye at baseline, %	33	Beta (alpha = 178, beta = 357)	AREDS report No. 11[10]
Monthly probability of developing CNV in fellow eye	0.0071	Beta (alpha = 4.98, beta = 677)	AREDS report No. 8[17]
Patients without health insurance, %, by age, y			
45 to 64	14.2	None	DeNavas-Walt et al,[11] 2007
≥65	1.5	None	DeNavas-Walt et al,[11] 2007
Monthly probability of treatment discontinuation			
Ranibizumab (ANCHOR)	0.00178	Beta (alpha = 3, beta = 1745)	ANCHOR (unpublished data, 2009)
Ranibizumab (MARINA)	0.00173	Beta (alpha = 5, beta = 2908)	MARINA (unpublished data, 2006)
PDT	0.00407	Beta (alpha = 7, beta = 1794)	ANCHOR (unpublished data, 2009)
Baseline VA letter score (SD) [approximate Snellen equivalent]			
Treated eye	46.5 (13.1) [20/125]	Empirical distribution based on trial data	ANCHOR[5]
Fellow eye without CNV at baseline	77.4 (13.7) [20/32]	Empirical distribution based on trial data	ANCHOR[5]
Fellow eye with CNV at baseline	34.5 (26.1) [20/200]	Empirical distribution based on trial data	ANCHOR[5]
Treated eye	53.5 (13.2) [20/80]	Empirical distribution based on trial data	MARINA[5]
Fellow eye without CNV at baseline	76.1 (14.7) [20/32]	Empirical distribution based on trial data	MARINA[6]
Fellow eye with CNV at baseline	38.6 (26.2) [20/160]	Empirical distribution based on trial data	MARINA[6]
VA change at 24 mo, mean (SD), letter score			
Primary eye, treated with ranibizumab	10.7 (16.5)	Empirical distribution based on trial data	ANCHOR[5]
Primary eye, treated with PDT	−9.8 (17.6)	Empirical distribution based on trial data	ANCHOR[5]
Primary eye, treated with ranibizumab	6.6 (16.5)	Empirical distribution based on trial data	MARINA[6]
Primary eye, sham treatment	−14.9 (18.7)	Empirical distribution based on trial data	MARINA[6]
Fellow eye with or without CNV at baseline	−3.6 (15.9)	Empirical distribution based on trial data	MARINA[6]
Fellow eye that developed incident CNV, treated with ranibizumab	6.6 (16.5)	Empirical distribution based on trial data	Assumed to have similar efficacy as in treated eye in MARINA[6]
Fellow eye that developed incident CNV, sham treatment	−14.9 (18.7)	Empirical distribution based on trial data	Assumed to have similar efficacy as in treated eye in MARINA[6]

(continued)

Table 1. Specification of the Model Parameter Values and Distributions Used for the Simulation (continued)

Parameter	Value	Distribution[a]	Source
Proportion (SD) of patients with VA letter score ≤38 (≤20/200) in incident eye after 2 y without treatment in ANCHOR-type cohort, %	67 (5.16)[c]	Beta	TAP report No. 3[18] based on patients with predominantly classic CNV; SD was estimated
Proportion of patients with VA letter score in better-seeing eye ≤38 (≤20/200), ie, legal blindness, after 2 y without treatment in ANCHOR-type cohort (variance), %	22.3 (0.05)[d]	Beta	TAP report No. 3[18]; ANCHOR[5]
Proportion (SD) of patients with VA letter score ≤68 (≤20/40) in incident eye after 2 y without treatment in ANCHOR-type cohort, %	97.0 (1.86)[e]	Beta	Assumption based on TAP report No. 3[18] for patients with predominantly classic CNV; SD was estimated
Proportion of patients with VA letter score ≤68 (≤20/40) in both eyes after 2 y without treatment in ANCHOR-type cohort (variance), %	52.6 (0.10)	Beta	Estimated based on information from TAP report No. 3[18]
Additional VA reduction for ranibizumab using reduced, fixed-frequency retreatment interval, mean (SD), letter score	–5.0 (1.0)[f]	Normal	PIER[7]; SD was based on an assumption
VA change per month after discontinuation from active treatment, letters	–1.6	None	Based on 2-y sham results in MARINA (–14.9 letters in 24 mo)[6]

Abbreviations: AMD, age-related macular degeneration; ANCHOR, Anti-Vascular Endothelial Growth Factor (VEGF) Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; AREDS, Age-Related Eye Disease Study; CNV, choroidal neovascularization; MARINA, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; NA, not applicable; PDT, photodynamic therapy; PIER, Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab; TAP, Treatment of Age-Related Macular Degeneration With Photodynamic Therapy; VA, visual acuity.

[a] The reported alpha and beta values characterize the shape of the gamma and beta distributions.

[b] The uncertainty around the point estimate of the incidence rates was not reported by Klein and colleagues; therefore, we estimated the numerator and denominator of the incidence rate, accounting for censoring from losses to follow-up, and calculated a 95% confidence interval for the estimated rate.

[c] This proportion was reported in the TAP report No. 3 using a VA letter score threshold of 33 or lower. The proportion of patients with a VA letter score of 38 or lower is expected to be larger; however, no adjustment was performed.

[d] Derived as the joint distribution of the proportion of patients with a VA letter score of 38 or lower in the first eye at 24 months without treatment and the proportion of patients with a VA letter score of 38 or lower in the fellow eye at 24 months without treatment.

[e] TAP report No. 3 disclosed that 12% of patients with predominantly classic CNV in the placebo group have a VA letter score between 54 and 73. It was assumed that 3% (one-fourth) have a VA letter score higher than 68.

[f] This amount of VA reduction for PIER dosing is in addition to the VA change at 24 months observed in the ANCHOR[5] and MARINA[6] studies.

whites in 2008 would develop neovascular AMD. Based on assumptions reported by the AREDS Group,[10] it is estimated that approximately one-third of these cases, or about 51 000 individuals, already had preexisting CNV in the fellow eye at the start of 2008.

CNV NOT REQUIRING RANIBIZUMAB

Approximately 2.5% of incident cases develop a symptomatic, well-demarcated extrafoveal CNV lesion for which laser photocoagulation as given in the Macular Photocoagulation Study[19] would be applied and in which recurrent CNV through the center of the macula would not occur. In such cases, ranibizumab need not be applied and visual acuity presumably would not decrease to 20/200 or worse. In addition, 20% of incident cases would have a fluorescein pattern that was occult with no classic CNV and without presumed recent disease progression, which includes the absence of visual acuity deterioration and therefore would not decrease to 20/200 or worse. Approximately 5% of cases would be predominantly hemorrhagic. Conservatively, if one assumed that all these predominantly hemorrhagic cases progressed to 20/200 or worse and that one-third of these developed similar disease in the second eye, one could also assume that 2553 individuals would become legally blind in a 2-year period because of the development of a predominantly hemorrhagic lesion in the second eye. Of the remaining incident cases, one can assume that 6% would not have access to monthly ranibizumab, leaving 103 582 (95% CI, 76 767 to 134 747) incident cases of CNV from AMD for which monthly ranibizumab would be indicated and accessible.

INCIDENT CASES OF LEGAL BLINDNESS

Based on the model designed for this study, if no treatment were applied to the 103 582 cases for which monthly ranibizumab is indicated and accessible, 16% (95% CI, 12% to 20%) or 16 268 (12 052 to 21 145) would progress to legal blindness in 2 years (**Table 2**). Monthly ranibizumab would reduce the incidence of legal blindness in 2 years by 72% (95% CI, 70% to 74%) to 4484 (3297 to 5854) or 4% (3% to 6%) of these individuals.

INCIDENT CASES OF VISUAL IMPAIRMENT

Based on the model designed for this study, if no treatment were applied to the 103 582 cases for which monthly ranibizumab is indicated and accessible, 34% (95% CI, 25% to 44%) or 34 702 (25 672 to 45 175) would progress to visual impairment in the better-seeing eye in 2 years (Table 2). Monthly ranibizumab would reduce the incidence of visual impairment in 2 years by 37% (95%

Table 2. Blindness and Visual Impairment Outcomes in Patients With Neovascular AMD With and Without Treatment With Monthly Ranibizumab

Scenario	No. (%) of Total Cohort (N = 103 582)	95% CI (%)	Relative Risk Reduction vs No Treatment (95% CI), %
Legal blindness[a]			
No treatment for CNV under center of macula	16 268 (16)	12 052 to 21 145 (12-20)	. . .
Ranibizumab indicated and accessible, monthly retreatment interval	4484 (4)	3297 to 5854 (3-6)	72 (70 to 74)
Visual impairment[b]			
No treatment for CNV under center of macula	34 702 (34)	25 672 to 45 175 (25-44)	. . .
Ranibizumab indicated and accessible, monthly retreatment interval	21 919 (21)	16 209 to 28 539 (16-28)	37 (35 to 39)

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; CNV, choroidal neovascularization.
[a] Defined as a best-corrected letter score of 38 or lower (approximate Snellen equivalent, ≤20/200) in the better-seeing eye.
[b] Defined as a best-corrected letter score of 68 or lower (approximate Snellen equivalent, ≤20/40) in the better-seeing eye.

Table 3. Blindness and Visual Impairment Outcomes With Alternative Treatment Strategies and With Outcomes by Eye

Scenario	No. (%) of Total Cohort (N = 103 582)	95% CI (%)	Relative Risk Reduction vs No Treatment (95% CI), %
Legal blindness[a]			
Ranibizumab indicated and accessible; reduced, fixed retreatment interval	6463 (6)	4722 to 8430 (5 to 8)	60 (57 to 63)
PDT indicated and accessible; no ranibizumab	14 408 (14)	10 677 to 18 752 (10 to 18)	11 (9 to 14)
Visual impairment, better-seeing eye ≤20/40[b]			
Ranibizumab indicated and accessible; reduced, fixed retreatment interval	28 857 (28)	21 235 to 37 538 (21 to 36)	17 (13 to 20)
PDT indicated and accessible; no ranibizumab	34 348 (33)	25 461 to 44 699 (25 to 43)	1 (–2 to 4)
Incident eye ≤20/200[c]			
No treatment for CNV under center of macula	56 819 (55)	41 912 to 73 680 (40 to 71)	. . .
Ranibizumab indicated and accessible; monthly retreatment interval	18 094 (17)	13 409 to 23 545 (13 to 23)	68 (66 to 70)
Ranibizumab indicated and accessible; reduced, fixed retreatment interval	23 030 (22)	16 937 to 30 056 (16 to 29)	59 (56 to 62)
PDT indicated and accessible; no ranibizumab	55 445 (54)	41 136 to 71 838 (40 to 69)	2 (–4 to 7)
Incident eye ≤20/40[d]			
No treatment for CNV under center of macula	61 665 (60)	45 636 to 80 154 (44 to 77)	. . .
Ranibizumab indicated and accessible; monthly retreatment interval	39 896 (39)	29 489 to 51 969 (28 to 50)	35 (34 to 36)
Ranibizumab indicated and accessible; reduced, fixed retreatment interval	47 120 (45)	34 823 to 61 327 (34 to 59)	24 (21 to 25)
PDT indicated and accessible; no ranibizumab	61 120 (59)	45 265 to 79 593 (44 to 77)	1 (–2 to 2)

Abbreviations: CI, confidence interval; CNV, choroidal neovascularization; PDT, photodynamic therapy.
[a] Defined as a best-corrected letter score of 38 or lower (approximate Snellen equivalent, ≤20/200) in the better-seeing eye.
[b] Defined as a best-corrected letter score of 68 or lower (approximate Snellen equivalent, ≤20/40) in the better-seeing eye.
[c] Defined as a letter score of 38 or lower.
[d] Defined as a letter score of 68 or lower.

CI, 35% to 39%) to 21 919 (16 209 to 28 539) or 21% (16% to 28%) of these individuals.

SENSITIVITY ANALYSES

If a reduced, fixed-frequency retreatment strategy were used (**Table 3**), the incidence of legal blindness in 2 years would decrease by 60% (95% CI, 57% to 63%) compared with no treatment to 6463 (4722 to 8430) or 6% (5% to 8%) of these 103 582 individuals. If PDT with verteporfin were applied to predominantly classic incident cases (Table 3), the percentage progressing to legal blindness in 2 years would decrease by only 11% (95% CI, 9% to 14%) to 14 408 (10 677 to 18 752) or 14% (10% to 18%) of these 103 582 individuals.

If a reduced, fixed-frequency retreatment strategy were used, the incidence of visual impairment in 2 years would decrease by 17% (95% CI, 13% to 20%) compared with no treatment to 28 857 (21 235 to 37 538) or 28% (21% to 36%) of these 103 582 individuals. If PDT with verteporfin were applied to predominantly classic incident cases, the percentage progressing to visual impairment

Table 4. Sensitivity Analyses of the Proportion of CNV Lesion Characteristics on Incident Cases of Legal Blindness in 2 Years

	Base Proportion, %	Cases of Legal Blindness (95% CI)	One-Half of Base Proportion, %	Cases of Legal Blindness (95% CI)	Twice Base Proportion, %	Cases of Legal Blindness (95% CI)
In the Setting of No Treatment						
Predominantly blood	5	16 268 (12 052 to 21 145)	2.5	16 696 (12 370 to 21 701)	10	15 412 (11 418 to 20 032)
Extrafoveal						
Laser then treatment after subfoveal recurrence	2.5	16 268 (12 052 to 21 145)	1.25	16 066 (11 906 to 20 872)	5	16 672 (12 343 to 21 690)
Laser and no subfoveal recurrence	2.5	16 268 (12 052 to 21 145)	1.25	16 477 (12 207 to 21 416)	5	15 851 (11 743 to 20 603)
Minimally classic and recent disease progression	10	16 268 (12 052 to 21 145)	5	16 165 (11 967 to 21 030)	20	16 474 (12 201 to 21 397)
Predominantly classic	20	16 268 (12 052 to 21 145)	10	14 299 (10 573 to 18 586)	40	20 207 (14 921 to 26 253)
Occult with no classic						
Recent disease progression at presentation	20	16 268 (12 052 to 21 145)	10	16 036 (11 869 to 20 880)	40	16 732 (12 386 to 21 746)
Recent disease progression in ≤1 y of presentation	20	16 268 (12 052 to 21 145)	10	16 036 (11 869 to 20 880)	40	16 732 (12 386 to 21 746)
No recent disease progression in ≤1 y	20	16 268 (12 052 to 21 145)	10	18 302 (13 559 to 23 746)	40	12 201 (9039 to 15 859)
In the Setting of Ranibizumab Treatment Where Indicated and Accessible						
Predominantly blood	5	4484 (3297 to 5854)	2.5	4602 (3384 to 6008)	10	4248 (3124 to 5546)
Extrafoveal						
Laser then treatment after subfoveal recurrence	2.5	4484 (3297 to 5854)	1.25	4447 (3270 to 5803)	5	4558 (3351 to 5950)
Laser and no subfoveal recurrence	2.5	4484 (3297 to 5854)	1.25	4542 (3340 to 5929)	5	4369 (3213 to 5704)
Minimally classic and recent disease progression	10	4484 (3297 to 5854)	5	4419 (3249 to 5769)	20	4614 (3391 to 6025)
Predominantly classic	20	4484 (3297 to 5854)	10	4124 (3025 to 5386)	40	5205 (3838 to 6801)
Occult with no classic						
Recent disease progression at presentation	20	4484 (3297 to 5854)	10	4338 (3192 to 5660)	40	4776 (3506 to 6232)
Recent disease progression in ≤1 y of presentation	20	4484 (3297 to 5854)	10	4338 (3192 to 5660)	40	4776 (3506 to 6232)
No recent disease progression in ≤1 y	20	4484 (3297 to 5854)	10	5045 (3710 to 6586)	40	3363 (2473 to 4391)

Abbreviations: CI, confidence interval; CNV, choroidal neovascularization.

in 2 years would decrease by only 1% (–2% to 4%) to 34 348 (25 461 to 44 669) or 33% (25% to 43%) of these 103 582 individuals.

Table 4 provides a series of outcomes for which the assumptions regarding the proportion of CNV lesion characteristics are individually doubled or halved in the model to determine the effect on the incidence of legal blindness for incident cases of CNV from AMD for which ranibizumab is indicated and accessible. Each analysis showed similar outcomes compared with those given in Table 2.

COMMENT

The mathematical model developed in this study indicates that ranibizumab as given in the MARINA[6] and ANCHOR[5] studies would reduce the number of cases of legal blindness in 2010 by 72% from approximately 16 000 to 4484 individuals with neovascular AMD for whom monthly ranibizumab would be indicated and accessible among the approximately 150 000 incident cases of eyes developing CNV from AMD in 2008. The impact of ranibizumab is at least as great when estimating the reduction in the magnitude of visual impairment in an individual (defined as ≤20/40 in the better-seeing eye). Furthermore, monthly ranibizumab when indicated and accessible greatly reduces the proportion of eyes that become 20/200 or worse or 20/40 or worse, regardless of the visual acuity in the fellow eye.

If this model assumes that, among the 151 340 incident cases of CNV in AMD, 2553 would be predominantly hemorrhagic cases with 20/200 or worse vision in the second eye and 6% (8280) would have incident CNV for which monthly ranibizumab was indicated but in which treatment was not accessible so that 16%, or 1325, would become legally blind within 2 years, then 3878 cases of incident CNV in AMD would progress to legal blindness regardless of the advances brought about by ranibizumab. However, another 16 268 cases of legal blindness in the absence of ranibizumab would be reduced by 72% to 4484, so that the total estimated number of cases of legal blindness among the 151 340 incident cases of CNV in AMD in 2008 would be reduced from 20 100 to approximately 8400 cases in 2010.

Following a similar logic with respect to visual impairment within 2 years, if this model assumes that, among the 151 340 patients with incident CNV in AMD, 6024 cases would involve predominantly hemorrhagic CNV with 20/40 or worse vision in the second eye and 6% (8280 patients) would have incident CNV for which monthly ranibizumab was indicated but not accessible so that 34%, or 2815, would have visual impairment within 2 years, then 8839 patients with incident CNV in AMD would become visually impaired regardless of the advances brought about by ranibizumab. However, another 34 702 cases of vision impairment in the absence of ranibizumab would be reduced by 37% to 21 919, so that the total estimated number of cases of visual impairment among the 151 340 incident cases of CNV in AMD in 2008 would be reduced by 29% from 43 541 to approximately 30 758 cases in 2010.

This model has several assumptions and weaknesses that require one to interpret the numbers put forth in this study as only an approximation. The incidence rates of CNV were based on a single study (the Beaver Dam Eye Study)[9]; however, that epidemiologic study had a large sample that characterized the natural history of the disease across 15 years and had been shown by other investigators[20] to be applicable to the general population. Racial subgroups other than non-Hispanic whites were not considered because there is limited information in the literature regarding incidence rates of CNV in other populations. The estimates in this model assume best-corrected visual acuity measurements on high-contrast charts; it is likely that visual acuity measurements in the better-seeing eye would be even worse without best correction or without high-contrast charts or both. These results also assume access to monthly ranibizumab for 2 years. Many clinicians consider withholding ranibizumab before completion of 2 years of monthly treatment based on effects seen on optical coherence tomography or fluorescein angiography or other parameters. However, several studies have suggested that outcomes are not as good as with monthly treatments[7,21-25] or are not adequately powered to determine whether outcomes are as good as with monthly treatments.[26] In addition, many clinicians consider substituting bevacizumab for ranibizumab, although the recently published analysis[27] of 1-year risks and benefits of every-4-week or less-frequent administration of bevacizumab coupled with every-4-week assessment has not been incorporated into this model. The results of the model in this study are derived from a time when a person's first eye may have lost substantial vision from CNV, before monthly ranibizumab became available in 2006. The impact of ranibizumab on reducing the incidence of legal blindness may be even greater if CNV is detected and treated promptly when a person's first eye develops CNV, before that eye sustains substantial vision loss, which was assumed to be approximately one-third of the incident cases of CNV in this model in 2008.

In summary, the number of cases of legal blindness (≤20/200 in the better-seeing eye) from neovascular AMD should be reduced dramatically if monthly ranibizumab were applied when indicated and accessible to patients, reducing the number of cases of legal blindness by approximately 70% to 74% and of visual impairment (≤20/40 in the better-seeing eye) by approximately 35% to 39%. This analysis suggests that the impact of neovascular AMD on uncorrectable legal blindness and visual impairment is dramatically reduced in individuals 50 years or older in the United States and throughout the world where access to monthly ranibizumab is available.

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