
Progression of visual loss and time between initial assessment and treatment of wet age-related macular degeneration

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ABSTRACT • RÉSUMÉ

Purpose: To determine whether the time elapsed from initial (referral) diagnosis of neovascular (wet) age-related macular degeneration (AMD) to assessment and treatment by a retinal specialist is associated with visual deterioration in the intervening period.

Methods: A prospective pilot study of 38 consecutive AMD patients who presented with newly diagnosed subfoveal choroidal neovascularization was conducted in a tertiary care retinal practice. All eligible subjects underwent clinical examination and digital fluorescein angiography at the time of assessment by a retinal specialist. Correlations were performed to assess the association between continuous independent variables and any visual deterioration since initial diagnosis. Multivariate linear regression models with stepwise techniques were used to evaluate any association between visual progression and time elapsed, while controlling for potential clinical covariates.

Results: Of the 38 patients, 32 (84%) met the inclusion and exclusion criteria; no differences in important variables were noted between those included and those excluded. The median time between initial diagnosis and referral assessment and treatment was 28 days (interquartile range = 36.5 days); some degree of visual loss developed in 14 (44%) of the subjects. The elapsed time was correlated with progression of visual loss ($r = 0.50$, $p = 0.003$). Multivariate linear regression demonstrated that only time elapsed and lesion type based on fluorescein angiography were associated with progression of visual loss ($R^2 = 0.491$, $F(4,28) = 6.744$, $p = 0.001$); lesion size, age and sex were not significantly associated with progression of visual loss.

Interpretation: Delay in assessment and treatment of new-onset wet AMD by a retinal specialist is associated with a higher risk of visual loss.

Objet : Établir si le temps écoulé entre le premier diagnostic (adresse) de la dégénérescence maculaire liée à l'âge (DMLA) exsudative et, d'autre part, l'évaluation et le traitement par un rétinologue est associé à la détérioration de la vue pendant le délai.

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Méthodes : Une étude pilote de cohorte portant sur 38 patients consécutifs atteints de la DMLA qui avaient un nouveau diagnostic de néovascularisation choroïdienne sousfovéale a été effectuée dans une clinique de soins tertiaires de la rétine. Tous les sujets admissibles ont subi un examen clinique et une angiographie numérique à la fluorescéine au moment de l'évaluation par un spécialiste de la rétine. L'on a effectué des corrélations pour estimer l'association entre les variables indépendantes continues et toute détérioration de la vue depuis le premier diagnostic. Les modèles multivariés de régression linéaire avec techniques séquentielles ont servi à évaluer toute association entre l'évolution de la vision et le temps écoulé, tout en contrôlant la possibilité de covariables cliniques.

Résultats : Parmi les 38 patients, 32 (84 %) ont satisfait les critères d'inclusion et d'exclusion; on n'a pas noté d'écart de variables importantes entre les inclus et les exclus. La durée moyenne entre le premier diagnostic et l'évaluation d'orientation et le traitement a été de 28 jours (écart interquartile = 36,5 jours); 14 patients (44 %) ont développé une perte de la vision. Le temps écoulé a été corrélé avec une progression de la perte visuelle ($r = 0,50$, $p = 0,003$). La régression linéaire multivariée a démontré que seulement le temps écoulé et le type de lésion selon l'angiographie à la fluorescéine ont été associés avec la progression de la perte visuelle ($R^2 = 0,491$, $F(4,28) = 6,744$, $p = 0,001$); la taille de la lésion, l'âge et le sexe ne furent pas associés de façon significative à la perte progressive de vision.

Interprétation : Le délai entre l'évaluation et le traitement d'une nouvelle DMLA exsudative par un spécialiste de la rétine est associé à un plus grand risque de perte de vision.

Age-related macular degeneration (AMD) is now the leading cause of visual loss in North America,¹ with choroidal neovascularization (CNV) accounting for 90% of cases of severe visual loss in these patients.² The prevalence and incidence of AMD will only increase as the demographic distribution of cohorts in the industrialized world shifts from left to right. Therefore, early detection of AMD with neovascularization will become necessary to ensure optimal effectiveness of treatment.³

In general terms, the burden of any disease can be measured in terms of its adverse effects on organs or senses, functional ability, quality of life, personal preferences and societal resources. AMD adversely affects vision through reductions in visual acuity and contrast sensitivity and the development of central scotomata.^{4,5} AMD also affects both visual function and health-related quality of life (HRQoL): investigators have demonstrated reductions in visual function with validated instruments that quantify visual function (the 14-item Visual Function questionnaire⁶ and the 25-item version of the Visual Function Questionnaire of the National Eye Institute, US National Institutes of Health⁷) and with generic instruments that measure overall HRQoL.⁸ In addition, there has been substantial research demonstrating the deleterious

effect of AMD on patient preferences.^{9,10} Using the time trade-off technique, investigators have found that the mean time that patients with AMD are willing to trade off to eliminate their visual dysfunction is correlated to visual acuity in the better-seeing eye; specifically, those whose vision from the better-seeing eye is 20/20 to 20/25 are willing to trade 11% of their remaining life, whereas those who are legally blind (have worse than 20/200 vision) are willing to trade 60% of their remaining lifetime in return for perfect vision.¹⁰

CNV is known to progress. In a prospective study of 80 patients with untreated CNV secondary to AMD, Klein, Jorizzo and Watzke¹¹ performed angiography at baseline and at a later date (mean time elapsed = 13 days). CNV growth rates ranged from 1 to 24 μm per day, with a mean progression of 10 μm per day; 54% of lesions displayed foveal growth. CNV growth was related to the interval between angiography sessions ($p < 0.0001$) but was not associated with the morphologic features of the CNV.

Vander, Morgan and Schatz,¹² studying 35 pairs of serial fluorescein angiograms from 30 consecutive patients with untreated subfoveal CNV, noted that the estimated growth rate of CNV in any single direction was 9 μm per day but that it was not possible to

reliably predict the growth rate from clinical parameters, which reinforced the recommendation for prompt evaluation of all subretinal CNV for the purpose of possible treatment.

Numerous clinical trials have been designed to evaluate the safety and efficacy of treatments for subfoveal CNV.^{13–16} Although these studies have clearly provided data on safety and efficacy, randomized clinical trials (RCTs) also provide highly valid data on the natural history of a condition. These trials are typically powered to detect clinically relevant outcomes at meaningful time points. Most of those designed to evaluate the safety and efficacy of treatments for subfoveal CNV are powered to detect visual acuity changes at 6 months, at 1 year and beyond. Accordingly, they offer little information on the natural history of untreated CNV in the very short term.

Microperimetry with the use of the scanning laser ophthalmoscope has recently been employed to better understand the natural history of subfoveal CNV secondary to AMD.¹⁷ This technique can measure progressive functional deterioration, as expressed by decreased fixation stability, loss of central fixation and impaired retinal sensitivity. These parameters are associated with initial visual impairment in AMD patients with secondary CNV. Fujii and colleagues¹⁷ found that within a subgroup of eyes with symptoms for 3 months or less, 11% lost central fixation and 42% showed a decrease in fixation stability.

The study presented here was conducted to evaluate the degree of visual loss that can occur in a short period, given the state of health care access in Canada. Specifically, we sought to determine whether a change in visual acuity occurred between the time of initial (referral) diagnosis and the time of assessment and treatment by a retinal specialist, as depicted in the conceptual model presented in Fig. 1.

METHODS

A prospective pilot study of 38 consecutive AMD patients who presented with newly diagnosed subfoveal CNV was conducted in a tertiary care retinal practice to evaluate whether the duration of the presence of neovascular (wet) AMD, defined as the time elapsed between initial (referral) diagnosis and assessment and treatment by a retinal specialist, was associated with any visual deterioration in the intervening period. This study, part of a larger one evaluating HRQoL and macular degeneration, was approved by

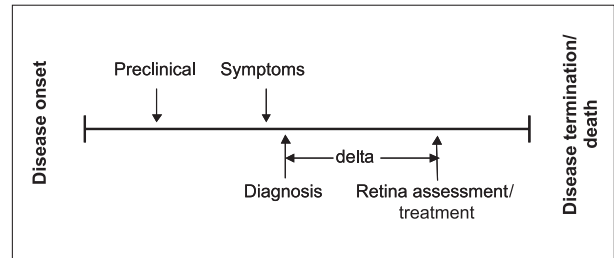


Fig. 1—Conceptual model of age-related macular degeneration (AMD).

the Institutional Review Board of Queen's University, Kingston, Ont.

Potential subjects were recruited from a tertiary care, hospital-based retinal practice. Eligible subjects were selected from a review of letters from referring doctors and represented a consecutive series of patients with presumed wet macular degeneration. If potential patients had new-onset wet AMD, as indicated in the referral letter, they were invited to participate in the study. Data on assessment and treatment by a retinal specialist were obtained prospectively, whereas information on the initial (referral) diagnosis was obtained retrospectively.

Patients were included in the study if they had new-onset wet AMD, defined as acute onset (< 30 days) of visual loss, visual distortion, changes in colour vision or development of central blurring of vision, in conjunction with angiographic evidence of subfoveal CNV. The type of lesion seen on angiography was not used as an exclusion criterion; patients were included if they had purely classic, predominantly classic, minimally classic or occult CNV. Patients were excluded from the study if their CNV was not related to AMD (i.e., if it was related to trauma, ocular histoplasmosis, myopia, angioid streaks, neoplasm, pattern dystrophy, inflammation or any other form of maculopathy).

All eligible subjects underwent clinical examination and digital fluorescein angiography. Those with angiographic evidence of diabetic macular edema or ischemia or intraocular pressure > 21 mm Hg were excluded from the study, as were those with significant lenticular opacification. Data on the dependent variable, visual acuity (calculated as the logarithm of the minimum angle of resolution [logMAR]), were recorded by a researcher masked to all clinical data, as was the angiographic assessment. Visual acuity at the point of retinal assessment and treatment was recorded at the time of clinical evaluation. Visual acuity at the

point of initial assessment was abstracted from the referral letter or from the hospital chart if the initial assessment was performed in one of our hospital's emergency or general eye clinics. All data were recorded on case report forms and input into an SPSS (Statistical Package for the Social Sciences) spreadsheet.

Continuous and categorical data were described in the usual fashion; means and standard deviations (SDs) were used to describe continuous variables, and proportions were used to describe categorical variables. Pearson correlations were performed to assess the associations between continuous, independent variables and any visual deterioration in the period between initial and retinal-specialist assessments. Multivariate linear regression models involving stepwise techniques were used to evaluate the association between visual progression and time between initial and retinal-specialist assessments; we controlled for potential clinical covariates, including age, sex, and size and type of lesion. All statistical analyses were performed by a statistician not involved in data abstraction.

RESULTS

Of the 38 patients who met our initial entry criteria (based on review of the referral letter), 6 were not included in the study: 2 had evidence of diabetic

retinopathy, 2 had evidence of ocular histoplasmosis, 1 had diabetic maculopathy without AMD, and 1 had pattern dystrophy. The other 32 patients (84%) met our inclusion and exclusion criteria; no differences in important variables were noted between those included in and excluded from the study.

Table 1 summarizes characteristics of the sample. The 32 patients had a mean age of 77 (SD 8.66) years, and 24 (75%) were female; 6% had purely classic membranes, 44% predominantly classic lesions, 19% minimally classic lesions and 31% occult CNV. Nearly all of the patients (94%) had evidence of macular degeneration in both eyes; most patients (72%) had the dry type (geographic atrophy) in their contralateral eye.

A significant difference in visual loss was noted when affected eyes were compared with their contralateral eye as a means of control (only 3% lost vision in the contralateral eye): the mean difference in the change in logMAR visual acuity between the 2 eyes was 0.343 ($p < 0.001$). Whereas 25% of the eyes with subfoveal CNV lost > 1 line of vision, no contralateral eye did so.

The median time elapsed between initial diagnosis and referral assessment and treatment was 28 days (interquartile range = 36.5 days); 14 (44%) of the subjects had some degree of visual loss, and 5 (16%)

Table 1—Characteristics of 32 patients with neovascular (wet) age-related macular degeneration

Variable	Mean	SD	Median	Quartiles 1, 3
Age (yr)	77.2	8.66	80	73.0, 84.5
Baseline VA				
Affected eye	20/125	NA	20/200	20/400, 20/65
Fellow eye	20/40	NA	20/40	20/200, 20/25
VA at treatment				
Affected eye	20/160	NA	20/200	CF, 20/100
Fellow eye	20/35	NA	20/30	20/80, 20/20
Lesion's greatest linear dimension (µm)	3654.2	1250.04	3350	2625, 4575
Time from diagnosis to treatment (d)	31.36	33.8	28.00	6.5, 43.0
Vision change in affected eye (no. of lines)	-1.0	1.52	0	-1.5, 0

Note: SD = standard deviation; VA = visual acuity; NA = not applicable; CF = counting fingers.

lost > 3 lines of distance visual acuity. The time between initial diagnosis and treatment was correlated with progression of visual loss ($r = 0.50$, $p = 0.003$) (Fig. 2). Multivariate linear regression demonstrated that only time elapsed and lesion type based on fluorescein angiography were associated with progression of visual loss ($R^2 = 0.491$, $F(4,28) = 6.744$, $p = 0.001$) (Table 2). The mean loss in logMAR visual acuity in the affected eye was 0.24; eyes with predominantly classic lesions were more likely than eyes with other lesion types to lose a significant amount of vision ($p < 0.002$). Lesion size, age and sex were not significantly associated with progression of visual loss ($p > 0.05$).

INTERPRETATION

Subfoveal CNV is associated with progressive visual loss. Numerous clinical trials have been conducted to evaluate the safety and efficacy of different treatments for subfoveal CNV secondary to AMD.¹³⁻¹⁶ Because these studies have been controlled, they have provided an excellent understanding of the natural history of this condition. The Macular Photocoagulation Study¹⁵ demonstrated that 11% of patients had a 6-line visual loss by 3 months, and the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) study¹⁴ showed that 24% had a 15-letter (3-line) loss by 3 months. The Anecortave Acetate Clinical Study Group¹³ recently demonstrated a mean logMAR change of 0.15 by month 3, and the VEGF Inhibition Study in Ocular Neo-

vascularization (VISION) Clinical Trial Group¹⁶ noted that 20% of those randomly assigned to usual care (sham injection ± verteporfin) had lost 3 or more lines of vision by 3 months. Our results demonstrating the rapid loss of vision in eyes with subfoveal CNV, combined with the results from research on fixation changes noted on microperimetry and scanning laser ophthalmoscopy, suggest the need for early assessment of suspected wet AMD and rapid treatment of the lesions.

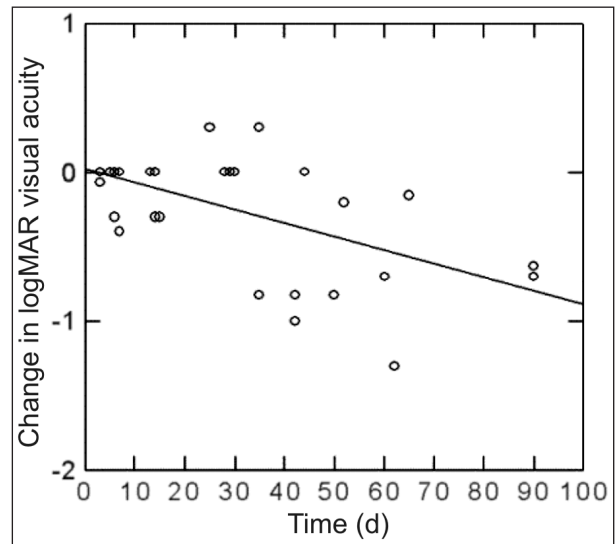


Fig. 2—Relation of degree of loss in visual acuity (calculated as the logarithm of the minimum angle of resolution [logMAR]) to time between initial diagnosis and specialist assessment and treatment.

Table 2—Coefficients of the regression model explaining the variance in change in the dependent variable, VA* in the affected eye, and the model’s overall fit with significant predictors

Variable	Sum of squares	df	Mean square	F	p value
Regression	2.40	4	0.60	6.744	0.001
Residual	2.49	28	0.09		
Total	4.88	32		$R^2 = 0.491$	
	Estimate	SE of estimate	t	95% CI	p value
Intercept	0.16	0.11	1.481	-0.062 to 0.384	0.150
Time elapsed	-6.74E-03	0.002	-4.148	-0.010 to -0.003	0.000
Lesion type	-0.41	0.122	-3.378	-0.659 to -0.162	0.002

Note: df = degrees of freedom; SE = standard error; CI = confidence interval.
*Calculated as the logarithm of the minimum angle of resolution (logMAR).

In December 2004, pegaptanib (Macugen), a 28-base RNA aptamer covalently linked to 2 branched 20-kD polyethylene glycol moieties, received approval from the US Food and Drug Administration (FDA) for the treatment of wet AMD. This treatment, along with photodynamic therapy with verteporfin, which has received FDA approval for the treatment of predominantly classic subfoveal CNV, slows progression of visual loss.^{14,16} Given that both treatments slow progression of disease as well as further visual loss, it is imperative that treatment delays not occur.

Our study was designed to determine whether visual acuity changes over short periods in patients referred for subfoveal CNV. The median time between initial diagnosis and retinal-specialist assessment and treatment of the lesion was 28 days. Within this period, 44% of patients lost some vision, and 15% lost > 3 lines of distance visual acuity; the mean loss in logMAR visual acuity in the affected eye was 0.24. When compared with the contralateral eye, the affected eye had a significantly greater change in visual acuity ($p < 0.001$).

In addition, our analysis demonstrated that predominantly classic CNV was significantly associated with progressive worsening of visual acuity. This finding supports the belief that these lesions are more aggressive and corroborates data from the TAP study showing that patients with this lesion type present with worse visual acuity and are more likely to demonstrate blood and blockage of fluorescein on angiography.¹⁸

The Canadian health care system is predominantly a single-payer system and theoretically allows for universal access; however, one of its limitations is the length of waiting lists for surgical procedures. Hatch and Trope¹⁹ studied the waiting lists for various ophthalmic interventions in Ontario and found those for retinal surgery and corneal transplantation to be 3.4 months and 11 months, respectively. An additional troubling statistic was the striking increase in length of the waiting lists over a 3-year period. To date, data on waiting lists for assessment and treatment of wet macular degeneration in Canada have not appeared in the peer-reviewed literature.

The US National Committee for Quality Assurance created the Health Plan Employer Data and Information Set (HEDIS) to measure quality of care delivered through various health care systems. Used by over 400 health plans, HEDIS is a set of standardized performance measures intended to help pur-

chasers and patients compare plans in terms of quality (instead of simply costs). HEDIS parameters consist of scores obtained for a given plan for each of 7 domains. One of these domains is access to care. HEDIS plans to add measurement of glaucoma services as an aspect of measuring the quality of care delivered by the various plans.^{20,21}

Although the concept of health report cards is emerging in Canada, particularly in cardiology,²² no data have been published on quality care and ophthalmology in this country. Given the rising prevalence and incidence of AMD, the availability of treatments that are either of proven benefit or in late-stage clinical trials, and the progressive nature of this condition, quality standards for the management of AMD will need to be developed. Our data, taken with those from previously published work, suggest that patients can lose vision from subfoveal CNV in a very short time. Given that progression of CNV can result in irreversible loss of vision and negatively affect HRQoL, we believe that delays in diagnosing and treating wet AMD are unacceptable. Factors that could reduce waiting times include a greater capacity to diagnose and treat patients with wet AMD, achieved through an increase in both human resources and capital equipment.

As with any study, ours has potential limitations. These include the fact that visual acuity measurement was not performed in a standardized fashion at the 2 times in the study (initial assessment and retinal-specialist assessment). We believe that this is not a significant threat to validity, as the change in vision in the control (contralateral) eyes was minimal: only 3% lost vision, compared with 44% of the eyes with CNV. Accordingly, we believe that the differences in visual acuity noted in the eyes with subfoveal CNV were real and not simply a manifestation of measurement variability or error. Another limitation of our study was that we measured only objective changes in distance visual acuity. There are other dimensions of vision, such as near acuity, contrast sensitivity and reading speed, that can affect HRQoL in patients with subfoveal CNV. Because the assessment of baseline vision was derived from data obtained from the referring doctors, these parameters could not be studied.

In summary, our study has demonstrated that even short delays in the diagnosis and treatment of new-onset wet AMD can result in significant loss of distance visual acuity. Especially with more effective treatments becoming available, our study suggests that early

assessment and treatment of new-onset wet AMD by a retinal specialist could help prevent vision loss.

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Key words: age factor, choroidal neovascularization, low vision, macular degeneration, pegaptanib, treatment delays