Review Article

The Natural History of Occult Choroidal Neovascularisation Associated With Age-related Macular Degeneration. A Systematic Review[†]

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Abstract

Introduction: The purpose of this review is to combine the results of existing literature on the natural history of occult choroidal neovascularisation (CNV) associated with age-related macular degeneration (AMD). Materials and Methods: Published reports evaluating eyes with occult CNV in AMD patients were selected for meta-analysis based on a computerised MEDLINE search. Pooled estimates of the proportions of eyes with a vision loss greater than 2 to 3 (moderate vision loss) or 6 lines (severe vision loss) at 1 year and 2 to 3 years, respectively, or developing a classic component on fluorescein angiography at 1 year were measured. Results: There is no significant heterogeneity among published rates of visual loss and development of classic CNV. The overall pooled estimates (95% confidence limits) of the proportions of eyes with at least moderate or severe vision loss, respectively, were 59% (53% to 64.5%) and 34% (25% to 43%) at 1 year and 70% (64% to 76%) and 47% (40% to 54%) at 2 to 3 years; the overall pooled estimate of the percentage of eyes developing classic CNV at 1 year was 46% (39% to 54%). Conclusion: A substantial number of patients with occult CNV from AMD will develop at least moderate visual loss at 1 year and severe visual loss within 3 years. However, visual acuity may remain stable in up to 30% of patients. These results may help us to understand the exact role of new therapies and in planning future trials.

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Key words: Age-related maculopathy, Fluorescein angiography, Meta-analysis

Introduction

Choroidal neovascularisation (CNV) is a leading cause of blindness in the western world. It causes 90% of the visual loss in age-related macular degeneration (AMD).[1] In selected subgroups of cases, laser photocoagulation of CNV can reduce the risk of severe visual loss compared with no treatment. However, the majority of neovascular lesions are not eligible for laser treatment under the current guidelines, because they are subfoveal, large or "occult" on fluorescein angiography. Recent reports suggested that photodynamic therapy with Visudyne (Novartis AG, Basel, Switzerland) might be beneficial not only for predominantly classic CNV from AMD, but also for selected occult subfoveal lesions. [2,3] A larger trial to confirm the benefits of Visudyne therapy in these lesions is currently underway.

Occult CNV, which is probably the most common angiographic appearance of neovascular AMD, has been reported to have a more benign prognosis than "classic" CNV by 2 retrospective studies and 1 small prospective study.[4-6] However, prospectively collected data from more recent randomised controlled trials have shown that a sizable percentage of cases who have already lost some vision will develop severe decreases in visual acuity.[7,8] Given the large number of patients presenting with this disease and the limited benefit of currently available therapies for occult CNV, discovering effective new treatments is important. Data regarding the natural history of occult CNV would be extremely helpful for planning clinical trials. The purpose of this study was to review systematically and combine the results of similar published randomised clinical trials (RCTs) and observational case

series (OCSs) reporting data on visual prognosis and disease progression of eyes with occult CNV.

Materials and Methods

To identify studies presenting data on the natural history of occult CNV, we searched MEDLINE using the terms "MeSH occult choroidal neovascularization" and "poorly defined choroidal neovascularization". The results of the search were screened; abstracts were reviewed by one of the authors (AP) for potentially relevant articles.

Articles were eligible for review if they fulfilled the following inclusion criteria:

1. The studies must have included in their analysis a series of eyes with AMD and occult CNV, observed for a minimum of 1 year.
2. The visual acuity outcome measures were reported for the occult CNV group or subgroup as the proportions of eyes with a specified number of letters/lines lost compared with the baseline examination.
3. The study must have been reported in English.

The literature search identified 136 original articles dealing with occult CNV in AMD patients. Ten met all the inclusion criteria and were included in the study.[2,4-12] Of these, 8 articles were RCTs and 2 were OCSs. Two articles of the RCTs reported data from the same patient population with different follow-up times and were therefore included in our analysis.[6,7] Similarly, 2 other articles were reports of the same RCTs analysed at different time points.[10,11] In all the OCSs, cases were collected and studied retrospectively over a defined time frame. Two studies, although reporting relevant data on the natural history of occult CNV, were excluded due to the wide variation in the follow-up periods, which would have been too long for pooling estimates with the other studies.[13,14]

When evaluating RCTs, data were obtained from the group of eyes with occult CNV randomly assigned to observation. If 2 subgroups of occult CNV, occult only and occult with classic component, were present in the same study, only data from eyes with occult only CNV were included in our review.

Visual loss was categorised as moderate vision loss (loss of at least 2 or 3 or more lines of visual acuity, depending on the study) and severe vision loss (loss of 6 or more lines). In order to assess the visual prognosis, we calculated the pooled percentage of eyes with at least moderate vision loss and severe vision loss for 2 separate time frames (1 year, 2 to 3 years) from all eligible studies for each time frame. Some studies reported rates for multiple time periods and therefore contributed to the pooled rates for both time frames. For the purpose of evaluating disease progression, we estimated the pooled rates of eyes developing a classic component on fluorescein angiography at 1 year. In fact, it

has been shown that the development of a classic component in patients who had occult CNV with no evidence of classic CNV at initial examination is associated with a poorer prognosis.[5]

We used a published meta-analysis technique to calculate the pooled percentage of eyes with at least moderate and severe vision loss for the 2 separate time frames and to estimate the pooled rates of eyes developing a classic component at 1 year.[15] We first performed a test for heterogeneity among study proportions using a test statistics Q of Cochran to determine the statistical diversity among the different sets of data for each time frame.[15] A *P* value of less than 0.05 was considered to indicate heterogeneity. We then estimated the pooled rates and their corresponding 95% confidence intervals (CIs). We used the general method of the weighted average to obtain a pooled estimate of the rate for each time frame from the observed rates of eligible studies. We used weights equal to the inverse of the sum of the within study variance and the among-study variance as proposed by DerSimonian and Laird.[15] The software package S-PLUS 2000 Professional was used for data analysis.

Results

The baseline characteristics of the eyes investigated in the 10 reports included in our analysis are given in Table 1. All the studies examined eyes with similar angiographic and functional characteristics. The majority of eyes had juxtafoveal CNV in only one study.[5] Symptoms at baseline caused by occult CNV were reported in 6 studies and 4 included a significant number of eyes with blood as part of the lesion (27% to 50%). Data on symptoms or evidence of blood were not reported by the remaining studies. The duration of follow-up was 1 year in 3 reports and 2 or 3 years in the remaining studies.

Figures 1, 2 and 3 depict the rate of at least moderate and severe vision loss and development of a classic component, along with their 95% CIs, for each study included in the analysis. No statistically significant heterogeneity was found for the different sets of data. The pooled rates (95% CI) for each time period are listed in Table 2.

Discussion

To our knowledge, no previous report has systematically reviewed data from published literature regarding the natural history of occult CNV in AMD patients. Occult CNV is an angiographic pattern, which has been redefined by the Macular Photocoagulation Study group in 1988, and represents an evolution in the interpretation of the angiographic entity previously known as "poorly defined" CNV.[16]

Data from retrospective as well as prospective studies were combined as observational data to assess the overall

Table 1. Baseline Characteristics of Eyes Included in the Meta-analysis by Initial Angiographic and Functional Features

| | Authors | Year | Design | No. of eyes | Angiographic characteristics of occult CNV, No. (%) of eyes | | | | Functional characteristics | | Follow-up duration (y) |
					Subfoveal	Juxtafoveal	Classic component	Evidence of blood	Initial median visual acuity	Symptoms	
1	Bressler et al[4]	1988	OCS	84	75 (89)	7 (8)	6 (7)	37 (44)	20/80	All	2-3
2	MPS Group[5]	1996	RCT	26	NR (25)*	NR (75)*	Absent	3 (11)	20/50	All	3
3$_a$	Bressler et al[6]	1996	RCT	26	All	None	NR	NR	20/80	All	1
3$_b$	Stevens et al[7]	1997		40			19 (48)	5 (12)	20/62		2
4	Guyer et al[8]	1996	OCS	18	All	None	Absent	NR	20/50-20/200	NR	1
5	RAD-S Group[9]	1999	RCT	59	All	None	Absent	NR	NR	All	1
6$_a$	TAP-S Group[10]	1999	RCT	20	All†	None	Absent	NR	NR	NR	1
6$_b$	TAP-S Group[11]	2001									2
7	Kobayashi and Kobayashi[12]	2000	RCT	7	Presumed‡	None	Absent	NR	20/63.7	NR	2
8	VIP-S Group[2]	2001	RCT	92	All	None	Absent	25 (27)	20/50	All	2

CNV: choroidal neovascularisation; MPS: Macular Photocoagulation Study; NR: not reported; RAD-S: Radiation Therapy for Age-related Macular Degeneration Study; TAP-S: Treatment of Age-related Macular Degeneration with Photodynamic Therapy Study; VIP-S: Verteporfin in Photodynamic Therapy Study;

* Data from both treatment and observation group; observation group-only data are not reported in the article, but the authors indicate that no imbalances of baseline characteristics between the 2 study groups were present.
† Data from eyes with occult CNV erroneously enrolled in the study, which should have included only eyes with evidence of classic CNV.
‡ Location of occult CNV not directly stated; lesions were included if they were judged unsuitable for laser photocoagulation under the MPS criteria.

Table 2. Pooled Estimates* of 1-year and 2- to 3-year rate of At Least Moderate and Severe Vision Loss and 1-year Rate of Development of Classic Choroidal Neovascularisation (and 95% Confidence Interval)

| | At least moderate vision loss† | | Severe vision loss‡ | | Development of classic CNV |
	1 year	2-3 years	1 year	2-3 years	1 year
Pooled estimates	58.9	70.1	33.7	47.2	46.3
95% CI	53.4-64.5	64.0-76.3	24.8-42.7	40.2-54.4	39.0-53.6

CI: confidence interval; CNV: choroidal neovascularisation

* Pooled rate estimates (%) were calculated as the weighted average of the observed study rates using the inverse total variance (sum of the within study variance and between study variance) as proposed by DerSimonian and Laird.[15]
† Loss of at least 2 or 3 lines; in 4 studies at least moderate vision loss corresponded to the loss of at least 2 lines. [5,7,8,12]

frequency estimate of at least moderate and severe vision loss at 1 and 2 to 3 years, respectively, and the development of classic CNV at 1 year in eyes with occult CNV. Because of the diverse nature of the studies, having similar, but not identical inclusion criteria and differing sample sizing, we used an established meta-analytic approach, the DerSimonian and Laird weights and variance formulation, accounting for the variability among studies.[15] In all cases, no statistically significant heterogeneity was found among the studies. Since the degree of observed heterogeneity, or statistical diversity, was very small, the pooled estimates should provide a good estimate of the overall frequency of moderate and severe vision loss and development of classic CNV. In addition, the narrow confidence intervals for the pooled estimates of the 2- to 3-year rate of at least moderate and severe vision loss make these estimates particularly precise, and thus representative of the true incidence. The pooled estimates indicated also an increase in frequency estimate over time for severe vision loss, with approximately 50% of patients experiencing severe vision loss by 2 to 3 years of follow-up. These data seem to reinforce the concept that visual prognosis of eyes with AMD and occult CNV is generally poor. However, up to 30% of eyes may retain stable vision.

There are, however, a number of limitations to our analysis. In particular, the number of studies included was small due to the scarcity of published reports on the natural history of occult CNV. Also, in 4 of these studies, the sample size was fewer than 25 cases.[5,8,10,12] Moreover, not all articles reported rates for all the time periods in which the studies were categorised, further decreasing the number of sets of data that were combined for each time frame. This

(a) At least moderate vision loss at 1 year

(b) At least moderate vision loss at 2-3 years

Bressler et al,[4] 1988 (n = 68)

Guyer et al,[8] 1996 (n = 8)

Stevens et al,[7] 1997 (n = 40)

RAD-S Group,[9] 1999 (n = 59)

TAP-S Group,[10] 1999 (n = 20)

VIP-S Group,[2] 2001 (n = 92)

Pooled proportion

0.0 0.2 0.4 0.6 0.8 1.0 1.2

Bressler et al,[4] 1988 (n = 68)

Bressler et al,[6] 1996 (n = 26)

MPS Group,[5] 1996 (n = 22)

TAP-S Group,[10] 1999 (n = 20)

Kobayashi and Kobayashi,[12] 2000 (n = 20)

VIP-S Group,[2] 2001 (n = 92)

Pooled proportion

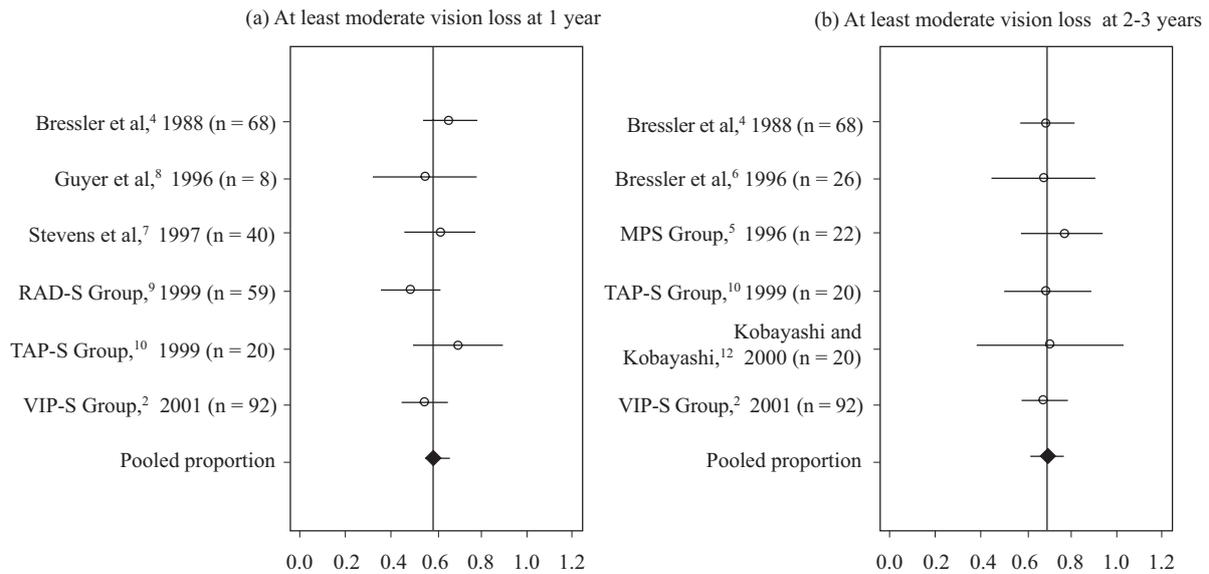0.0 0.2 0.4 0.6 0.8 1.0 1.2

Fig. 1. Individual and combined proportions of eyes with at least moderate vision loss: (a) at 1 year, (b) at 2 to 3 years. Studies, identified by principal author or study group and year of publication, are arranged in chronological order (by year of publication). n: number of subjects in each study; horizontal bars: 95% confidence interval for the proportion; vertical line: overall pooled proportion of eyes with at least moderate vision loss at 1 year for all studies combined, using the DerSimonian and Laird[15] method of moment estimate of the pooled rate. Test statistics Q for heterogeneity (5 degrees of freedom) = 5.70 ($P = 0.33$) at 1 year and test statistics Q for heterogeneity (5 degrees of freedom) = 0.77 ($P = 0.98$) at 2 to 3 years.

(a) Severe vision loss at 1 year

(b) Severe vision loss at 2-3 years

Bressler et al,[4] 1988 (n = 68)

MPS Group,[5] 1996 (n = 26)

Stevens et al,[7] 1997 (n = 40)

TAP-S Group,[10] 1999 (n = 20)

VIP-S Group,[2] 2001 (n = 92)

Pooled proportion

0.0 0.2 0.4 0.6 0.8 1.0 1.2

Bressler et al,[4] 1988 (n = 46)

Bressler et al,[6] 1996 (n = 26)

MPS Group,[5] 1996 (n = 22)

VIP-S Group,[2] 2001 (n = 92)
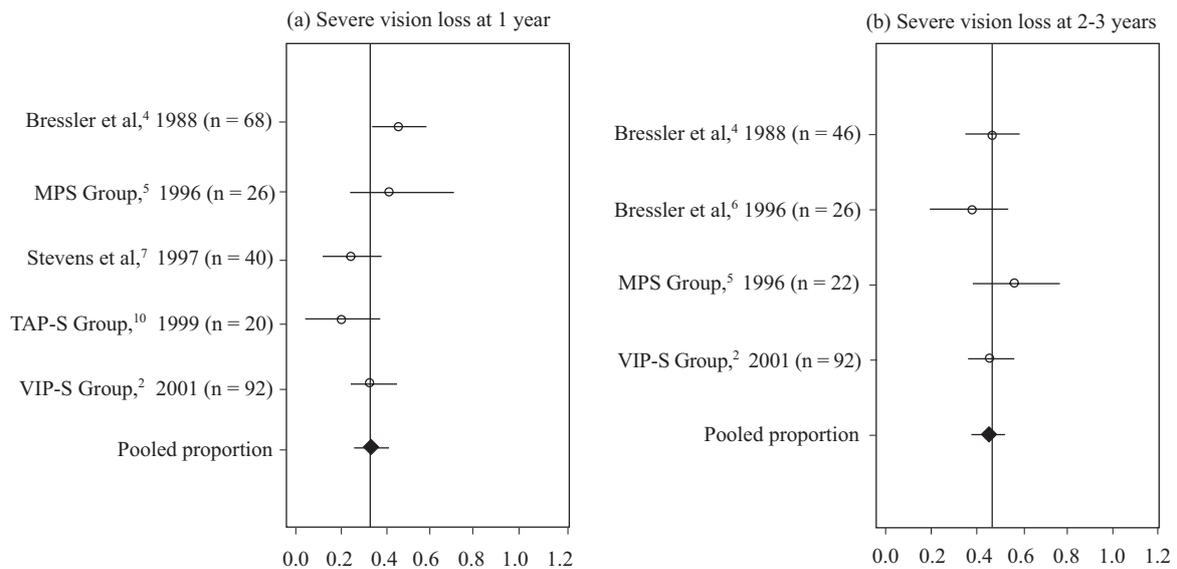
Pooled proportion

0.0 0.2 0.4 0.6 0.8 1.0 1.2

Fig. 2. Individual and combined proportions of eyes with severe vision loss: (a) at 1 year, (b) at 2 to 3 years. Test statistics Q for heterogeneity (4 degrees of freedom) = 9.64 ($P = 0.05$) at one year and test statistics Q for heterogeneity (3 degrees of freedom) = 2.14 ($P = 0.54$) at 2 to 3 years.

may explain the rather wide confidence interval for the pooled estimates of the 1-year rate of development of classic CNV. A basic assumption of meta-analysis is that all patients and endpoints are comparable. In our analysis, differences in the angiographic and functional characteristics of the study population, in the assessment and definition of visual loss and in the follow-up times could constitute potential sources of variability among studies. However, the majority of the studies used angiographic definitions adapted from the Macular Photocoagulation Study Group[16] in their inclusion criteria for occult CNV and only 2 studies were published prior to the final Macular Photocoagulation Study guidelines for interpretation of fluorescein angiograms and may have therefore investigated slightly different cases.[4,5] Furthermore, in 8 of the 10 reports, visual acuity was assessed using ETDRS charts.[2,5,6,7-12] In only one study,[5] the majority of patients enrolled had juxtafoveal occult CNV
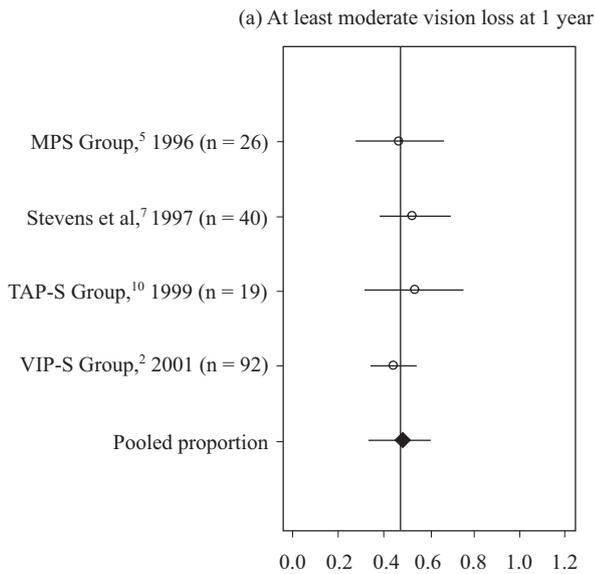
(a) At least moderate vision loss at 1 year

Fig. 3. Individual and combined proportions of eyes developing classic choroidal neovascularisation at 1 year. Test statistics Q for heterogeneity (3 degrees of freedom) = 1.49 (P = 0.68).

instead of subfoveal and in 3 studies a classic component was present, potentially influencing the natural course.[4,6,7] In addition, data on visual symptoms at presentation and signs of presumed recent disease progression, such as evidence of blood, generally considered indicators of poor prognosis, are lacking from 3 and 5 studies, respectively. Therefore, relatively stable forms of disease might have been included in these studies. Vision outcomes were expressed as the proportions of eyes with at least 3 or 6 lines lost in most of the publications, with the exception of 4 studies, in which at least moderate vision loss corresponded to the loss of at least 2 lines, potentially increasing the rates of eyes losing vision in this category.[5,7,8,12] Finally, follow-up times did not vary considerably within and among studies. In 4 of the 6 studies analysed in the 2- to 3-year time frame category, the follow-up was 2 years.[2,6,11,12]

The assessment of visual prognosis could have also been determined by calculating the pooled proportions of eyes with absolute levels of visual acuity at each time period. A meta-analysis on the proportion of eyes with visual acuity worse than 20/200 or better than 20/40 would have also provided clinically valuable information, particularly in advising patients. However, we could not perform such analysis due to the scarcity of studies reporting these proportions, although the visual acuity distribution in those RCTs in which it was reported, was very similar. In particular, the proportions of eyes with visual acuity equal to or worse than 20/200 were, respectively, 51% and 33% at 1 year in the RCT by Bressler et al[6] and in the Verteporfin in Photodynamic Therapy Study (VIP-S)[2] and 50%, 61%

and 45% at 2 to 3 years in the Macular Photocoagulation Study (MPS)[5], RCT by Bressler et al[6] and the VIP-S;[2] the proportions of eyes with visual acuity equal or better than 20/40 were, respectively, 9% and 6.5% at 1 year in the RCT by Bressler et al[6] and in the VIP-S[2] and 9%, 4% and 6.5% at 2 to 3 years in the MPS,[5] RCT by Bressler et al[6] and in the VIP-S.[2]

The results of our analysis apply only to the angiographic pattern investigated in the reports that we explored, in which CNV, based on Macular Photocoagulation Study group definitions, occupies more than 50% of the entire "lesion". Neovascular lesions in which thick blood obscuring normal choroidal fluorescence or a serous detachment of the retinal pigment epithelium (PED) occupies an area greater than the occult CNV are therefore excluded. Occult CNVs presenting in association with a serous PED are not so uncommon and their presence may be difficult to determine on fluorescein angiography, due to the rapid fluorescein pooling beneath the retinal pigment epithelium. Recently, indocyanine green videoangiography has been able to improve delineation of these forms of occult CNV, and some reports have suggested that their visual prognosis and response to therapy may be worse.[8,17-20] Their inclusion in the definition of occult CNV may therefore further increase our pooled rates of visual loss over time. On the other hand, 5 out of 8 studies included in our analysis investigated eyes with signs or symptoms of presumed recent disease progression and may not be representative of the entire population of occult CNV. Thus, eyes with occult CNV, good vision and no symptoms, subretinal blood, fluid or lipid exudation, may have a different natural history.

The finding that the visual acuity remained stable in up to 30% of patients over a 2- to 3-year follow-up time suggests that distinct forms of occult CNV convey a variable prognosis for vision. The use of fluorescein angiography alone to classify these lesions therefore seems to be insufficient and the additional information provided by indocyanine green angiography or other new imaging techniques may become useful in better categorising these lesions. Recently, indocyanine green angiography has allowed us to better delineate and clarify the nature of particular vascular abnormalities, such as polypoidal choroidal vasculopathy, retinal choroidal anastomoses and retinal angiomatous proliferations, presenting on fluorescein angiography as occult CNV in a large percentage of cases.[21-24] The natural history of these lesions has very little documentation, but preliminary reports suggest that it may differ from other forms of occult CNVs.

In summary, by quantitatively summarising data from previous reports, this analysis provides valuable information on the natural history of occult CNV. It confirms that the

occult angiographic appearance of CNV in AMD patients has a negative, even if not uniform, influence in the visual prognosis of this disease. Approximately 70% and 50% of the eyes presenting with this angiographic pattern develop at least moderate and severe vision loss, respectively, within 3 years of follow-up and 46% of these eyes develop a classic component within 1 year. Given the observed homogeneity among the studies included in our analysis, these data represent a reasonable estimate of the true incidence of visual loss and development of classic CNV and may be useful for the interpretation of results of uncontrolled trials and for planning future trials. However, the highly variable course of these lesions makes it difficult to speculate on the natural history of occult CNV in uncontrolled trials and additional diagnostic tools need to be introduced to provide a better classification, which is more predictive of the visual prognosis.

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