A Randomized Clinical Trial of a Single Dose of Intravitreal Triamcinolone Acetonide for Neovascular Age-Related Macular Degeneration

One-Year Results

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Objective: To determine if a single intravitreal injection of 4 mg of triamcinolone acetonide in patients with classic choroidal neovascularization associated with age-related macular degeneration can safely reduce the risk of severe visual loss.

Methods: A double-masked, placebo-controlled, randomized clinical trial was performed in patients 60 years or older who had choroidal neovascularization with any classic component, a duration of symptoms of less than 1 year, and a visual acuity of 20/200 or better. Best-corrected visual acuity, intraocular pressure, and cataract grading were performed before the injection and then at 3, 6, and 12 months.

Main Outcome Measure: The development of severe loss of vision (30 letters) by survival analysis on an intention-to-treat basis.

Results: One hundred fifty-one eyes were randomized into the study, and follow-up data were obtained for 73 (97%) of the 75 eyes in the treated group and for 70 (92%) of the 76 eyes in the control group. There was no difference between the 2 groups for the development of severe visual loss during the first year of the study (log-rank $\chi^2_1=0.03$, $P=.90$). In both groups, the 12-month risk of severe visual loss was 35%, with a hazard ratio of 1.05 (95% confidence interval, 0.59-1.86). The change in size of the neovascular membranes, however, was significantly less in eyes receiving triamcinolone than in those receiving placebo 3 months after treatment ($P=.01$), although no difference was noted after 12 months. After 12 months, treated eyes had a significantly higher risk of an elevated intraocular pressure (31/75 [41%] vs 3/76 [4%]; $P<.001$), but not of cataract progression ($P=.29$).

Conclusions: A single dose of intravitreal triamcinolone had no effect on the risk of loss of visual acuity during the first year of the study in eyes with age-related macular degeneration and classic choroidal neovascularization, despite a significant antiangiogenic effect found 3 months after treatment. This biological effect warrants further study.

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NEOVASCULAR age-related macular degeneration (ARMD) is the most frequent cause of blindness in the developed world. The Blue Mountains Eye Study,[1] for example, found that 1.2% of the population 49 years or older had choroidal neovascularization (CNV). The prevalence increased to 19.6% in those 85 years or older.[1] Similar prevalence rates were found in the Beaver Dam Eye Study.[2] Anticipated increases in life expectancy have made the identification of preventive and more efficacious treatment strategies for neovascular ARMD one of the most pressing issues in ophthalmology.

Laser treatment and photodynamic therapy with verteporfin are the only interventions that have been demonstrated by randomized clinical trials to reduce the risk of visual loss in eyes with neovascular ARMD. Conventional laser photocoagulation is beneficial for extrafoveal neovascularization,[3] but it is apparent that fewer than 15% of patients with ARMD who are initially seen with CNV are eligible for conventional laser treatment that will not destroy their central vision.[4] Photodynamic therapy with verteporfin is helpful for many patients with CNV beneath the fovea, reducing the overall risk of moderate visual loss 2 years after treatment from 62% to 47%.[5,6]

Early studies suggested that the corticosteroid triamcinolone acetonide might be an effective treatment for CNV. Intravitreally injected triamcinolone, together with its commercial vehicle, has been well tolerated by eyes of rabbits[7] and monkeys.[8] The intravitreal administration of corticosteroids has been effective in re-

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ducing the incidence of laser-induced subretinal neovascularization in primates[9] and rats.[10] The outcome of 30 eyes of 28 patients with subfoveal exudative ARMD who had received treatment with intravitreal triamcinolone was studied. Six months after receiving treatment, the visual acuity (VA) had not significantly deteriorated in 26 (87%) of the eyes.[11] After 18 months, only 6 (23%) of these 26 eyes experienced severe visual loss.[12] No serious adverse effects of a single injection of triamcinolone were detected. While laser treatment excites local inflammation, which may increase the risk of recurrence of CNV, corticosteroidal agents might be expected to reduce tissue edema and to inhibit subretinal fibrosis in addition to any antiangiogenic effect they might exert.

We report herein the 1-year results of a prospective, single-center, double-masked, placebo-controlled, randomized clinical trial to test the hypothesis that a single intravitreal injection of 4 mg of triamcinolone will reduce the risk of severe visual loss in eyes with ARMD that have classic CNV and symptoms of less than 1-year duration.

METHODS

PATIENT ENROLLMENT

Patients were recruited from the Retina Unit of the Sydney Eye Hospital, which is a major public tertiary referral center. The inclusion criteria were as follows: (1) 60 years or older; (2) diagnosed as having ARMD with CNV with any classic component (≤3.5 Macular Photocoagulation Study [MPS] disc areas subfoveally or within 199 µm from the foveal center); (3) laser treatment discussed with patient, and patient declined; (4) clear media; (5) VA of 20/200 or better; and (6) duration of symptoms no longer than 12 months. The exclusion criteria were as follows: (1) other serious eye diseases, including diabetic retinopathy, hypertensive retinopathy, macular dystrophy, angioid streaks, high myopia (>8 diopters), glaucoma (with glaucomatous field loss), epiretinal membranes, macular hole, and nystagmus; (2) the use of systemic corticosteroids (prednisolone, ≥5 mg/d) or any drug that affects the macula, including chloroquine, hydroxychloroquine sulfate (Plaquenil Sulfate), thioridazine, and chlorpromazine; (3) any condition, physical, mental, or social, that would affect regular follow-up; and (4) any condition that would prevent photographic or angiographic documentation.

Patients were deemed to be enrolled in the study after they had signed the informed consent form; standard fundus photographs, including fluorescein angiograms, had been taken; and the treatment allocation had been issued by the independent designated officer in the clinic.

TREATMENT ASSIGNMENT

A randomization schedule with variable block sizes was produced using a list of computer-generated pseudorandom numbers. This was kept in a locked cabinet in the clinic as a series of cards folded in half and inserted into sealed, opaque, numbered envelopes. After a patient had enrolled into the study by signing the consent form, which was approved by the South Eastern Sydney Area Health Service Research Ethics Committee, Eastern Section, the surgeon who was to administer the treatment was given the next in the series of envelopes by a designated member of the clinic staff. Neither the surgeon nor the designated member of staff was otherwise involved in the study. For patients with both eyes eligible, the first eye was randomly allocated and the other eye received the other treatment, apart from the first 2 such patients.

MASKING

The initial study design stipulated that patients allocated to no treatment were not to receive any placebo treatment. Because it quickly became apparent that many of these patients were unlikely to continue in the study despite counseling (2 patients assigned to no treatment dropped out of the study), a placebo treatment was introduced after the 12th patient had been enrolled; the placebo consisted of a subconjunctival injection of isotonic sodium chloride solution. To mask patients to their treatment assignment, they were advised that floaters, which are prominent after an injection of triamcinolone, might occur after an injection of placebo and the active study medication. It was recognized that the development of corticosteroid-related adverse events might unmask the clinical observers. To reduce the impact of this, the measurement of best-corrected VA, the main outcome measure, was performed when the patients arrived at the clinic, without reference to their previous notes and before a medical history was taken. Photographic outcomes were analyzed by a grader (W.C.) trained by the Blue Mountains Eye Study Reading Centre who was masked to treatment assignment. The presence of crystals in the color photographs unmasked this grader to treatment assignment in 12 patients. These crystals were not, however, evident in the angiograms, which were analyzed before the color photographs.

TREATMENT

Intravitreal triamcinolone was injected into the vitreous within 1 week of the baseline angiogram and on the day of the baseline VA measurements. The procedure was performed in a minor procedures area in the outpatient clinic under sterile conditions. Eyes were prepared with 20 µL of 0.25% apraclonidine hydrochloride, several applications of 20 µL of 1% tetracaine, and 40 µL of 5% povidone-iodine (Betadine). A small amount of 2% lidocaine was then administered subconjunctivally with a 30-gauge needle to the site of the injection, and the intraocular pressure (IOP) was reduced by digital massage. Triamcinolone acetonide, 40 mg/mL (0.1 mL of Kenacort 40; Bristol-Myers Squibb Pharmaceuticals, Noble Park, Victoria, Australia), was injected into the vitreous 5 minutes later using a 27-gauge needle. A small amount of 1% chloramphenicol ointment was then instilled.

OUTCOMES

The primary outcome measure was the rate of development of severe visual loss (≥30 letters on a logMAR chart). Changes in (1) size and (2) leakage of neovascular membranes on fluorescein angiography were secondary outcome measures. A minimum sample size of 130 patients was required for 90% power of detecting as significant, at the 2-sided 5% level, a reduction in the risk of severe visual loss over 2 years from 55% to 25%, allowing for 10% dropout.

GRADING OF FLUORESCEIN ANGIOGRAMS

All photographs and angiograms were analyzed using a standard grading system developed at the Blue Mountains Eye Study Reading Centre. All angiograms were reviewed by 2 masked independent graders (W.C. and P.M.), and any differences between the 2 graders were resolved by open discussion. Baseline angiograms for all enrolled patients were assessed for adherence to the eligibility criteria. Patients who did not adhere to the eligibility criteria remained in the data analysis.

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Table 1. Patient Characteristics at Baseline*

Characteristic	Triamcinolone Acetonide–Treated Group (n = 75)	Placebo Group (n = 76)
Female sex	43 (57)	49 (64)
Hypertension	31 (41)	40 (53)
No. of letters read		
≥54	32 (43)	34 (45)
35-53	43 (57)	42 (55)
Mean (range)	51.6 (35-77)	51.8 (35-80)
Smoking history†		
Never	37 (49)	34 (45)
Previous	27 (36)	26 (35)
Current	11 (15)	15 (20)
Age, mean, y	76	77

*Data are given as number (percentage) of patients in each group unless otherwise indicated.

†Data for this characteristic were missing for 1 patient in the placebo group.

Angiographic features, including classic and occult patterns of CNV and subfoveal, juxtafoveal, and extrafoveal classification, were based on MPS guidelines.[13] Total lesion size (including blocked fluorescence, subretinal fibrosis, serous detachment of the retinal pigment epithelium, and contiguous blood) was measured using modified MPS disc area templates as overlays. In addition, side-by-side comparisons of follow-up angiograms with baseline films were used to determine changes in CNV size and fluorescein leakage, which was assessed by expansion of hyperfluorescence in late frames of the angiogram, relative to CNV size in early frames.

DATA COLLECTION

Patient data were reviewed by masked observers (W.L. and M.C.G.) before treatment and then at 3, 6, and 12 months. The best-corrected VA was measured using a protocol adapted from the MPS manual,[14] with a self-calibrating logMAR chart that used a backlight (Lighthouse International, LaSalle, Ill) at 2.40, 0.95, and 0.60 m. The IOP was also determined, and cataracts were graded using a semiquantitative scale (0-4+) with the aid of photographic standards from the Age-Related Eye Disease Study. Stereocolor photographs of the macula were taken before treatment and then at 6 and 12 months. Fluorescein angiography was performed at baseline and at 3 and 12 months. Patients were also seen 1 and 6 weeks after treatment by their usual ophthalmologist for determination of the IOP and Snellen VA. Data were entered onto standard data collection forms and transferred to an electronic database by dual data entry. Source data verification was performed by 2 independent study monitors for all patients for eligibility, demographic, and all outcome data (excluding photographic data).

Safety data were reviewed periodically by a Safety Monitoring Committee. This committee was instructed to consider suspending the trial if a significant ($P<.01$) difference between the 2 groups in the development of grade 3 (severe) adverse events was found. The study was approved and monitored by the ethics committees of the University of Sydney and the South Eastern Sydney Area Health Service, Eastern Section.

STATISTICAL ANALYSIS

Data were analyzed on an intention-to-treat basis 12 months after the last patient was treated. Patients were regarded as having developed severe visual loss if their VA at 12 months (or at their last visit before that if they missed the 12-month visit) had decreased since enrollment by at least 30 letters. The time they developed severe visual loss was regarded as the first visit at which their VA had decreased by 30 letters or more. Eyes that lost 30 letters or more at the 3- or 6-month visit, but had lost fewer than 30 letters at the 12-month visit, were not recorded as having experienced severe visual loss. Patients were regarded as unavailable for follow-up if they died or withdrew from the study before the first follow-up, at the 3-month visit. Thereafter, they were regarded as censored at the time they were last seen. The time to developing severe visual loss in treated and control eyes was compared using the log-rank test for all patients with follow-up data. Cox proportional hazards regression analysis was used to estimate the hazard ratio and to adjust for potential confounding variables. To calculate Kaplan-Meier survival curves and estimated 12-month risk of severe visual loss, follow-up times between 10.5 and 14.0 months were recoded as 12. Angiographic and photographic outcomes were analyzed using the Fisher exact test. Changes in CNV size and leakage at 3 months were analyzed using a χ^2 test for trend in proportions for eyes in which the result was known. No allowance was made in the analysis for possible correlation between paired eyes of the same individual, because only 12 patients had both eyes treated in the trial.

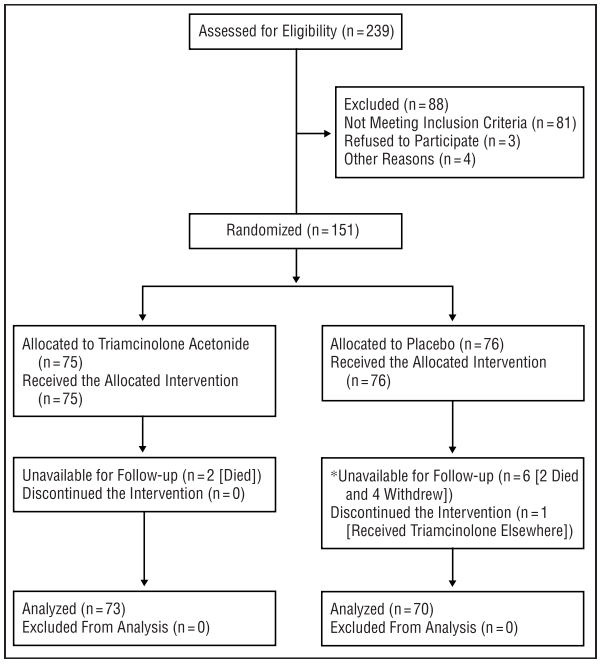


Figure 1. Flowchart of the patients in the first year of the Intravitreal Triamcinolone Study. The asterisk indicates that no follow-up data were obtained for these patients.

RESULTS

In total, 139 patients had 151 eyes treated in the trial, 75 with triamcinolone and 76 with placebo. Baseline patient demographic data are shown in **Table 1**. The 2 groups of patients were similar, with a slight preponderance of patients in the placebo group being women and having a history of systemic hypertension. **Figure 1** shows the flow of patients through the first year of the study.

Lesion characteristics at baseline are shown in **Table 2**. Lesions were similar among the 2 groups. Most neovascular membranes were totally classic.

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Table 2. The CNV Lesion Characteristics at Baseline*

Characteristic	Triamcinolone Acetonide–Treated Group (n = 75)	Placebo Group (n = 76)
Not CNV	1	2
% Classic		
100	50	50
51-99	8	8
1-50	14	12
0	2	4
CNV location		
Subfoveal	58	54
Juxtafoveal	11	18
Extrafoveal	5	2
CNV size (MLD), µm		
≤1500	22	27
1501-3000	37	29
>3000	15	18

Abbreviations: CNV, choroidal neovascularization; MLD, maximum linear dimension.
*Data are given as number of patients in each group.

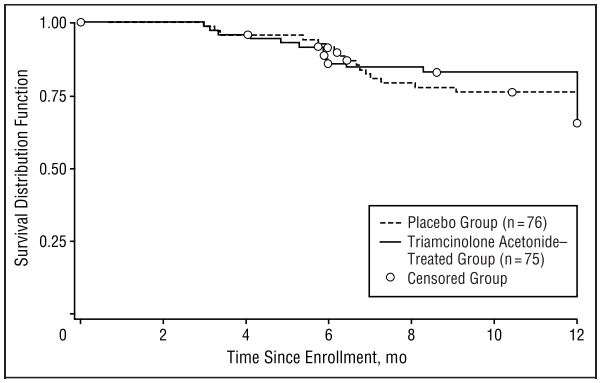


Figure 2. Survival curve of severe vision loss in patients in the triamcinolone acetonide–treated group and the placebo group.

The rate of development of severe visual loss was practically identical in the 2 groups, as shown in **Figure 2** (hazard ratio, 1.05; 95% confidence interval, 0.59-1.86; log-rank $\chi^2_1=0.03$, $P=.90$). The 12-month risk of severe visual loss was 35% (95% confidence interval, 23%-46%) in both groups. No evidence of a beneficial effect was seen at 3 or 6 months after treatment. A Cox proportional hazards regression analysis to adjust for the effect of smoking or hypertension did not alter this result. The rate of development of moderate visual loss (15-29 letters) 3 and 12 months after treatment was also similar between the 2 groups (**Table 3**).

In view of the divergence of these results from previous studies that had reported a beneficial effect of intravitreal triamcinolone on the visual outcome in patients with CNV, we examined potential confounding influences. The first was the possibility that the drug was inactive or had not been given correctly. In this case, one would predict that eyes in the treated group that exhibited an elevation of IOP (and, therefore, were likely to have received the active drug correctly) would have had a better outcome than those that did not. **Figure 3** shows the development of severe visual loss of eyes that exhibited an elevation of IOP of 5 mm Hg or higher vs the untreated fellow eye compared with those eyes without an elevated IOP in the group receiving intravitreal triamcinolone. There was no significant difference between the 2 groups ($P=.91$). Another possibility was that a beneficial effect of the treatment on the macula had been masked by the development of a corticosteroid-related cataract. In this case, it would be expected that pseudophakic eyes in the active treatment group would have done better than phakic eyes. **Figure 4** shows that this was not the case.

Despite the lack of effect of active study treatment on the rate of development of severe visual loss, an analysis of the fluorescein angiograms suggested that intravitreal triamcinolone exerted an antiangiogenic effect. Three months after treatment, more eyes in the active treatment group had smaller or unchanged neovascular membranes compared with eyes receiving placebo ($P=.01$) (**Figure 5**). **Table 4** shows the distribution of lesion size at baseline and 3 months. At baseline, most lesions had a greatest linear dimension of less than or equal to 3000 µm, and the treated group had fewer small lesions. Three months after treatment, there was a slight nonsignificant tendency for treated eyes to have small and medium lesions ($\chi^2_1=0.20$, $P=.66$). No difference was found between the 2 groups for lesion size or growth 12 months after treatment (data not shown), nor in change in the amount of leakage from the neovascular lesion at 3 months (**Figure 6**) or 12 months (data not shown) after treatment. Of the 2 variables, change in size seemed to be a more reliable indicator of angiogenic effect, because the significance of finding reduced leakage when the size of the neovascular membrane had increased dramatically was not clear. There were 49 (32.5%) and 43 (28.5%) of the 151 eyes in which a grading of change in size or leakage, respectively, could not be made (unknown) because of patient death or dropout, because of insufficient quality of the angiograms, or because the patient declined the 3-month angiogram. The visual outcome between treated and untreated eyes designated unknown for the grading of change in size and leakage was not significantly different ($P=.87$; data not shown).

Table 5 summarizes adverse events in the 2 groups during the first year of the study. There were no moderate or severe adverse events associated with either the intravitreal injection or the subconjunctival placebo. Treated eyes had a significantly increased risk of an elevated IOP, but not of cataract progression. The Safety Monitoring Committee was satisfied that all adverse events associated with intravitreal triamcinolone could be and were adequately managed in this study. A detailed analysis of the safety data for the entire study will appear elsewhere.

COMMENT

This randomized, double-masked, placebo-controlled clinical trial was undertaken to assess the potential usefulness of a single injection of 4 mg of intravitreal triamcinolone in preventing severe loss of vision in eyes with ARMD and classic CNV. No difference in the rate of development of severe visual loss was detected when pa-

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Table 3. Frequency Distribution of Changes in Visual Acuity From Baseline by Treatment and Visit*

	3-mo Follow-up		12-mo Follow-up	
	Triamcinolone Acetonide–Treated Group (n = 68)	Placebo Group (n = 64)	Triamcinolone Acetonide–Treated Group (n = 69)	Placebo Group (n = 65)
>1-Line increase	6 (9)	7 (11)	2 (3)	4 (6)
≤1-Line increase to <3-line decrease	42 (62)	39 (61)	25 (36)	20 (31)
≥3-Line decrease to <6-line decrease	15 (22)	14 (22)	18 (26)	19 (29)
≥6-Line decrease	5 (7)	4 (6)	24 (35)	22 (34)

*Data are given as number (percentage) of patients in each group.

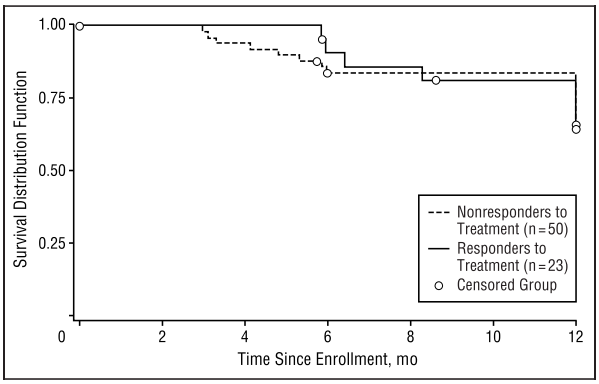


Figure 3. Survival curve of severe vision loss in patients receiving triamcinolone acetonide by intraocular pressure response to the corticosteroid.

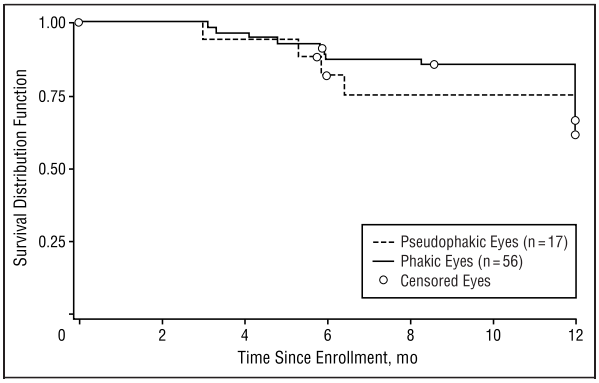


Figure 4. Survival curve by lens status at baseline.

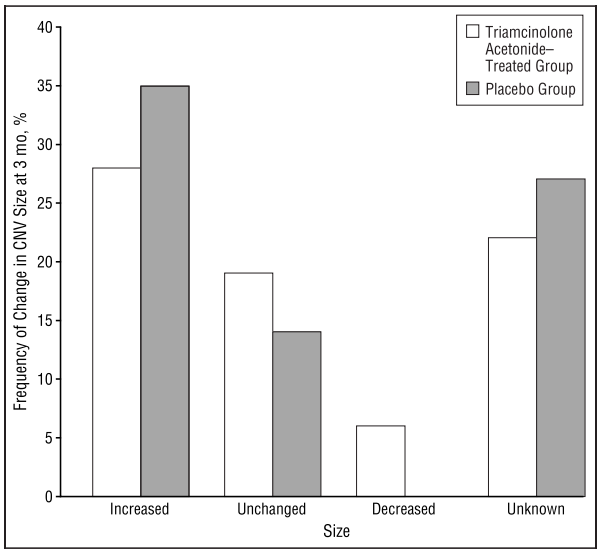


Figure 5. Change in choroidal neovascularization (CNV) at 3 months. Data for the test for trend are as follows: $\chi^2_1=6.20$, $P=.01$ (excluding those unable to be graded [unknown]).

Table 4. Distribution of Lesion Size (Maximum Linear Dimension) at Baseline and 3 Months*

Lesion Size, µm	Triamcinolone Acetonide–Treated Group (n = 74)	Placebo Group (n = 74)
Baseline		
≤1500	22 (30)	27 (36)
1501-3000	37 (50)	29 (39)
>3000	15 (20)	18 (24)
3 mo		
≤1500	13 (18)	8 (11)
1501-3000	22 (30)	18 (24)
>3000	20 (27)	28 (38)
Unknown	19 (26)	20 (27)

*Data are given as number (percentage) of patients in each group. Percentages may not total 100 because of rounding.

tients receiving active treatment were compared with those receiving placebo after 12 months of follow-up. The lack of any difference did not seem to be due to difficulties in administering the treatment, nor did any beneficial effect seem to be masked by the development of corticosteroid-related cataract.

An interesting secondary outcome of this study was noted on analysis of the growth of the CNV during the first 3 months of the study through the masked evaluation of fluorescein angiograms. A significant antiangiogenic effect of intravitreal triamcinolone was demonstrated in eyes that received active study medication. The distribution of lesion size 3 months after treatment was not significantly different among the treated and placebo groups, but there were fewer small lesions in the treated group to begin with. The prospectively identified secondary outcome was change in size, and this was significantly less in the treated group. Why the inhibition of vessel growth did not result in improved VA in treated eyes is not certain, but because the precise mechanism by which vision is lost in patients with subretinal neovascularization is poorly understood, it is reason-

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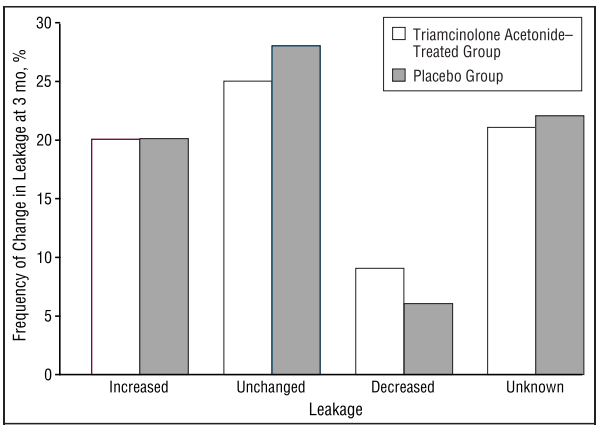


Figure 6. Change in leakage at 3 months. Data for the test for trend are as follows: χ^2_1=0.18, P=.70 (excluding those unable to be graded [unknown]).

Table 5. Adverse Events Related to Treatment After 12 Months*

Adverse Event	Triamcinolone Acetonide–Treated Group (n = 75)	Placebo Group (n = 76)	*P* Value
Procedure related			
Absent	70	73	.49
Present	5	3	
Corticosteroid-related events			
Intraocular pressure increase			
Absent	44	73	<.001
Present	31	3	
Cataract formation			
Absent	53	30	.29
Present	4	0	
Other			
Moderate	1†	0	.50

*Data are given as number of patients in each group. Data for all patients were not available for all events.
†This was a hemiretinal vein occlusion.

able to suggest that simple growth of the neovascular frond is only one contributory factor. Although this biological effect was not sustained through to the 12-month assessment, it warrants further study. It raises questions as to whether patients in earlier stages of CNV, such occult neovascularization, may benefit from treatment with intravitreal triamcinolone. It leaves unanswered whether a higher dose of intravitreal triamcinolone given more frequently, or in combination with other treatments such as photodynamic therapy, might be efficacious for the treatment of classic CNV.

Assumptions on the risk of visual loss in untreated patients for this study were based on data from a controlled study of laser treatment of subfoveal CNV in patients with ARMD conducted by the MPS Group.[15] The enrollment criteria for this study were similar to our own, with the exception that the VA for the MPS could be as poor as 10/200, whereas we included eyes with a VA of 20/200 or better. In the MPS, the risk of severe visual loss of eyes with a VA of 20/200 or better was 45% after 2 years, compared with 23% in a preliminary series[11] performed by some of us of 26 eyes treated with intravitreal triamcinolone. The MPS of juxtafoveal membrane treatment found severe visual loss in 54% of untreated eyes after 2 years.[16]

The results of this study contradict those of previous studies[11,17] that suggested a beneficial effect of intravitreal triamcinolone therapy for CNV. These 2 clinical trials were limited to fewer than 30 patients each. The design and conduct of the present study are more comprehensively described than those of its predecessors. It is also a considerably larger study, although with 75 patients per group, it does not exclude a smaller effect than the reduction of risk of severe visual loss from 55% to 25% that we chose to measure. In the animal studies[9,10] that have been reported, intravitreal triamcinolone was given at the same time as an intense laser burn was used to induce CNV. It is not clear how accurately this model reflects established CNV in patients with ARMD. Laser-induced CNV presumably has a prominent inflammatory component that might make it more susceptible to treatment with corticosteroids. Moreover, when the corticosteroid is given at the same time as laser therapy, it could act to prevent the development of CNV rather than to treat existing CNV. This model might serve better as a rationale for the use of intravitreal triamcinolone for the prevention of recurrence of CNV after it has been ablated by argon laser or photodynamic therapy.

It is unlikely that the results of this study were biased by a difference between the treated and control groups. In fact, eyes in the 2 groups were remarkably similar for demographic characteristics, VA, and CNV size and type at baseline. More than three quarters of the CNV in the treatment and placebo groups in this study was 100% classic, compared with only 40% in the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy Study,[6] which had similar enrollment criteria. The reason for this is not clear, but likely reflects a bias of referring retinal specialists who might have preferred to treat predominantly occult neovascularization conservatively.

All efforts were taken to adhere to a double-masked design in this study. Treated patients were potentially marked if there was asymmetric elevation of the IOP or if they complained of floaters. The primary outcome variable, VA, was the first observation made at each visit by an independent refractionist, before the measurement of IOP and without reference to the case report form. Floaters almost always subsided by the 3-month visit, which was the first visit for the formal measurement of VA. Presumably, the crystals had dropped out of the visual axis by then. Nevertheless, it is difficult to ensure complete double masking with this intervention. The crystals were occasionally seen by the masked grader of photographs, and some patients may well have suspected that they had received treatment, although untreated patients were probably not aware of their allocation because patients were informed on enrollment into the study that floaters did not always occur.

The weaknesses of this study include a relatively limited number of clinical outcomes and possible underdosing. Other measures of visual function, such as reading speed and contrast sensitivity, may be additional useful predictors of disability in patients with ARMD.[18] Although an effect

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on these secondary outcomes without any effect on best-corrected VA, which remains the gold standard, would scarcely have justified the use of the drug as a primary intervention for CNV in patients with ARMD, it might have guided the further evaluation of whether the intervention was useful in patients with less advanced forms of the disease or in combination with other treatments.

The duration of an intravitreal injection of 4 mg of triamcinolone is not known. In the present study, glaucoma medication was discontinued in 15 (71%) of the 21 eyes that required it after receiving triamcinolone after a mean of 8.0 months (data not shown). It seems reasonable, therefore, to believe that significant levels of triamcinolone are likely to persist inside the eye for at least 4 months. Before commencing the present study, we had thought that a second injection produced an unacceptable rate of adverse events.[11] We have since observed that the incidence of adverse events after a second injection seems to be similar to that accompanying a single injection as long as there is an interval of at least 4 months between the 2 injections (M.C.G. and W.L., unpublished data, 2002). Data from preliminary studies had suggested that a single injection might have had a beneficial effect that lasted longer than the presence of the drug, possibly by tipping the balance in favor of regression of the exudation and scarring that accompanied subretinal neovascularization. The present study does not support this contention. It is possible that a second injection 4 to 6 months after the first in the present study might have been more efficacious.

The dose of 4 mg of triamcinolone that is commonly used clinically seems to have been chosen as the largest volume of the strongest commercially available solution that can be safely injected into the human eye. A dose escalation study should be considered if further evaluation of the intravitreal triamcinolone is planned.

This study failed to show that a single intravitreal injection of 4 mg of triamcinolone prevents severe loss of vision over 12 months in eyes with ARMD and classic CNV. It does not, however, preclude the possibility that the drug might be found more effective at a higher, or more sustained, dose. The significant inhibition of the growth of neovascular fronds found 3 months after treatment suggests that randomized clinical trials of intravitreal triamcinolone might be considered for less advanced forms of CNV, particularly occult CNV, or in conjunction with other forms of treatment, such as argon laser or photodynamic therapy. The 2-year results of this study will be described and analyses provided after the effect of removing the corticosteroid-induced cataracts is determined.

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