Intravitreal Reinjection of Triamcinolone for Exudative Age-Related Macular Degeneration

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Objective: To evaluate the outcome of repeated intravitreal injections of triamcinolone acetonide for the treatment of exudative age-related macular degeneration.

Methods: This prospective, comparative nonrandomized clinical interventional study included 13 patients with progressive exudative age-related macular degeneration with occult, or predominantly occult, subfoveal neovascularization. All patients had shown an increase or stabilization of visual acuity after a first intravitreal injection of 25 mg of triamcinolone acetonide. They received a second intravitreal injection of 25 mg of triamcinolone acetonide 3.1 to 18 months after the first injection. Mean±SD follow-up time after the second injection was 5.2±3.6 months (median, 5.3 months). A control group included 24 patients with exudative age-related macular degeneration who did not receive treatment for their maculopathy. The main outcome measures were visual acuity and intraocular pressure.

Results: In the study group, mean±SD visual acuity increased significantly (P=.005 and P=.003, respectively) from 0.17±0.11 to 0.32±0.26 and from 0.15±0.14 to 0.23±0.19, respectively, after the first and second injections. An increase in visual acuity was found for 10 patients (77%) after the first and second injections. In the control group, visual acuity did not vary significantly during follow-up (P=.81). The difference in change in visual acuity between the study group and control group was significant (P=.01 [Snellen lines] and P=.05 [logMAR units]). The peak in visual acuity and, in a chronologically parallel manner, the peak in intracocular pressure elevation occurred 2 to 5 months after each injection.

Conclusions: Repeated intravitreal injection of 25 mg of triamcinolone acetonide may lead to an increase in visual acuity in patients with exudative age-related macular degeneration, with the peak in visual acuity and intraocular pressure elevation occurring about 2 to 5 months after each injection.


A GE-RELATED MACULAR DEGENERATION is the most common irreversible cause of severe loss of vision in the elderly population in Western countries.1,2 Ocular photodynamic therapy with verteporfin has been demonstrated to reduce vision loss in patients with the classic or predominantly classic type of exudative age-related macular degeneration.3 Despite its importance for quality of life of the individual patient and its marked socioeconomic effect on society, therapy for age-related macular degeneration has remained unsatisfactory for many patients with occult subfoveal neovascularization.

The purpose of this study was to investigate whether the antiangiogenic, antiproliferative, and antiedematous effects of triamcinolone acetonide would improve visual acuity in patients with exudative age-related macular degeneration.4,6 Because previous studies had not shown a therapeutically positive effect of topical, oral, or intravenous application of cortisone, we chose the intracocular injection of cortisone to achieve high levels of steroids at the site of required action without provoking major systemic adverse effects.

In a previous pilot study of patients with exudative age-related macular degeneration with occult or predominantly occult subfoveal neovascularization, intravitreal triamcinolone was associated with a significant increase in mean visual acuity 2 to 3 months after the injection.7 Mean visual acuity declined toward the baseline values 3 to 5 months after the injection. Patients who had responded favorably to the first injection received a reinjection when the visual acuity decreased after an initial increase. The purpose of this study was to report the outcomes of the latter patients who received a reinjection of intravitreal triamcinolone for the treat-
ment of exudative age-related macular degeneration and to compare the patients in this study group with those in a control group who received no treatment for exudative age-related macular degeneration.

**METHODS**

The study group in this prospective, comparative nonrandomized clinical interventional investigation included 13 consecutive patients (13 eyes; 9 women; 7 right eyes) who had a progressive decrease in visual acuity due to exudative age-related macular degeneration with occult or predominantly occult subfoveal neovascularization; who had received an intravitreal injection of 25 mg of triamcinolone acetonide; who had shown an increase or stabilization in visual acuity after the injection; and who experienced a rereduction in visual acuity several months after the injection. The study included all eyes for which an intravitreal reinjection of triamcinolone was performed as treatment for exudative age-related macular degeneration. The reinjection took place at a mean ± SD duration of 7.2 ± 1.1 months (median, 6 months; range, 3.1-18 months) after the first intravitreal injection. Mean ± SD follow-up time after the second injection was 5.2 ± 3.6 months (median, 5.3 months; range, 1.3-13.3 months). Mean ± SD age of the patients was 79.1 ± 8.3 years (range, 64.6-100.5 years; median, 79.0 years). Refractive error ranged between -1.0 diopter (D) and 3.5 D (mean ± SD, 1.33 ± 1.59 D). Mean ± SD intraocular pressure prior to the first injection was 16.1 ± 3.6 mm Hg (median, 15 mm Hg). All patients were fully informed about the experimental character of the therapy and signed a consent form. The ethics committee of the university approved the study, which followed the tenets of the Declaration of Helsinki.

The control group in the study included 24 patients (24 eyes; 16 women; 13 right eyes) who had exudative age-related macular degeneration but did not receive an intravitreal injection of triamcinolone or any other treatment for this disease. The reason for assigning these patients to the control group was that they did not want an intravitreal injection even though it was offered to them. Mean ± SD refractive error was 1.56 ± 2.08 D (range, -2.50 D to 6.13 D), and mean ± SD age was 78.5 ± 8.7 years (range, 59.2-92.8 years; median, 78.0 years). Mean ± SD visual acuity at baseline measured 0.17 ± 0.11 (Snellen charts) (range, 0.03-0.30) and 0.85 ± 0.31 logMAR units.

Because of the distribution of patients in the study and control groups, these groups did not vary significantly in preoperative visual acuity (P=.29), preoperative intraocular pressure (P=.52), age (P=.99), refractive error (P=.62), sex (P=.59), right or left eye (P=.63), or length of follow-up (P=.86). All patients were fully informed about the experimental character of the treatment.

Fluorescein angiography revealed subfoveal choroidal neovascularization located mainly (>50% of the whole membrane) or completely underneath the retinal pigment epithelium in all eyes. None of the eyes included in the study underwent cataract surgery after the first intravitreal injection, neither as a single procedure nor as a combined procedure with the second injection.

All patients in the study group received an intravitreal injection of 25 mg of crystalline triamcinolone acetonide in 0.2 mL of Ringer lactate solution. Prior to the intravitreal injection, topical 5% povidone-iodine (Alcon, Ft Worth, Tex) was applied. The triamcinolone had been prepared by extracting 0.62 mL from the ampule (Volon A; Bristol-Myers-Squibb, Munich, Germany) containing 40 mg of triamcinolone acetonide in 1 mL. The extracted volume was placed into a tuberculin syringe (1 mL) filled with Ringer lactate solution. A millipore filter (pore size, 5 µm; Sterifix Pury; Braun Melsungen AG, Melsungen, Germany) was placed on top of the syringe, and most of the contents of the syringe were pressed through the filter, with the triamcinolone crystals remaining in the syringe. The syringe was then refilled with Ringer lactate solution, and the same procedure was repeated 3 times. At the end, 0.2 mL of solution was left in the syringe and was injected transconjunctivally into the vitreous cavity.

Patients in the study group were reexamined the first day after the injection, about 1 week after the injection, and in approximate monthly intervals after that. Patients in the control group were reexamined in approximate 2-month intervals. Visual acuity (Snellen) was determined in a standardized fashion by an observer performing best-corrected refractionometry.

Statistical analysis was performed using commercially available software (SPSSWIN version 11.5; SPSS Inc, Chicago, Ill). Significance was set at P=.05 (2-tailed) for all statistical tests.

**RESULTS**

After the first injection, mean ± SD visual acuity had significantly (P=.003; Wilcoxon rank sum test) increased from 0.17 ± 0.11 (median, 0.20; range, 0.03-0.30) to a maximum of 0.32 ± 0.26 (median, 0.30; range, 0.04-0.90) (Figure 1). Expressed in Snellen lines, 6 eyes (46%) increased in visual acuity by 2 or more. Converting visual acuity measurements to logMAR units showed a change from 0.88 ± 0.70 to 0.67 ± 0.42 logMAR units. The increase in visual acuity was statistically significant for the measurements obtained 2 months after the injection (P=0.04). For the measurements performed 1 month after the injection, the difference between the baseline visual acuity and postinjection visual acuity was marginally significant (P=.09). Because of the selection of patients for the study, an increase in visual acuity was found in 10 (77%) of 13 patients. Three (23.1%) of 13 patients...
Figure 2. Boxplot showing visual acuity measurements prior to and after the second intravitreal injection.

**COMMENT**

Treatment of exudative age-related macular degeneration with occult or predominantly occult subfoveal neovascularization has been inconclusive so far. In contrast
to the classic type of subfoveal neovascularization, for which photodynamic therapy with verteporfin has been shown to stabilize or increase visual acuity. photody-
namic therapy has been less successful for the treatment of occult subfoveal neovascularization.1 As an alterna-
tive to laser treatment, Penfold et al8,9 and Challa et al10 started to inject triamcinolone intravitreally in an effort to treat exudative age-related macular degeneration. Simi-
larly to Challa and colleagues, Danis et al11 performed a comparative study and reported a beneficial effect of tri-
amcinolone in the study group compared with the control group. Additionally, Ranson et al12 applied intravit-
real triamcinolone for the treatment of recurring subfoveal choroidal neovascularization after laser treatment. A re-
cent investigation including 71 eyes with exudative age-
related macular degeneration demonstrated a signifi-
cant increase in visual acuity after an intravitreal injection of 25 mg of triamcinolone acetonide.7 The improve-
ment in visual acuity was significant for the examina-
tions performed 1 month (P = .04) and 2 months (P = .04) after the injection. About 3 to 5 months after the injec-
tion, visual acuity declined so that measurements ob-
tained at the end of the follow-up period for that study did not differ significantly (P = .17) from the baseline val-
es. Overall, however, 48 eyes (66.2%) had gains in vi-
sual acuity during the follow-up period.

In our study, patients were re-treated with an intra-
vitreal injection of 25 mg of triamcinolone acetonide if the first intravitreal injection was associated with stabiliza-
tion or increase in visual acuity. The results suggest that the reinjection led to a significant (P = .003) improve-
ment in visual acuity, with 10 (77%) of 13 patients show-
ing an increase in visual acuity during the follow-up pe-
riod. That figure was comparable with the frequency of improvement in visual acuity after the first injection in the same patients (10/13 [77%]). One may infer that eyes that have shown a beneficial effect with 25 mg of intravitreal triamcinolone acetonide may receive an intravitreal rein-
jection if the visual acuity deteriorates again. Our find-
ings confirm those of a previous case report describing a patient who received 5 intravitreal injections of 25 mg of triamcinolone acetonide and who after each injection dem-
onstrated a reincrease in visual acuity.13

Interestingly, the peak of the increase in visual acu-
yty occurred about 2 to 5 months after the injections, with no marked difference in the time of peaks between the first injection and reinjection (Figures 1 and 2). This sug-
gests that a reinjection of triamcinolone may be per-
formed about 3 to 5 months or more after an initial in-
jection if the first is associated with an increase in visual acuity. In a chronologically parallel manner, the peak of the elevation in intraocular pressure was about 2 to 5
months after the injection. This shows that after an in-
vitreal injection of triamcinolone, patients must un-
dergo close follow-up for several months to detect a ste-
roid-induced increase in intraocular pressure. Besides the chronological correlation between an increase in visual acuity and an elevation in intraocular pressure, the postin-
jection increase in visual acuity was statistically inde-
pendent of the elevation in intraocular pressure.

There are limitations to this study. The number of patients treated was relatively small; however, the postin-
jection visual acuity measurements were significantly bet-
ter than the baseline values when all patients with an in-
vitreal reinjection were included. Thus, the small num-
ber of patients may support our conclusions. An-
other important limitation of the study is its design as a nonrandomized comparative investigation. Because the first intravitreal injection of triamcinolone was associ-
ated with an increase in visual acuity, it was difficult to con-
vince patients to take part in a randomized trial in which some of them might not receive treatment. Fur-
thermore, comparing the patients in the study group with those in the control group showed significant differ-
ences in the change in visual acuity during follow-up. This suggests that the reincrease in visual acuity after the sec-
ond injection of triamcinolone was caused by the treat-
ment and not the natural course of the disease.

Another limitation of the study is the method used to measure visual acuity. Instead of the charts used for the Early Treatment Diabetic Retinopathy Study,14 visual acu-
ity was determined using Snellen charts in a standardized fashion by an observer performing best-corrected refrac-
tometry. However, the same method for assessment of vi-
sual acuity was applied to the study group as well as the control group, so this flaw in the study methods might have been partially compensated for. A further limitation is that although intravitreal triamcinolone may increase cata-
ract, cataract surgery was not performed in combination with or after the intravitreal injection. The vision-
reducing effect of progressive cataract may have hidden a vision-improving effect of triamcinolone, so again this limi-
tation of the study may support its conclusion.

An additional limitation of our study may be the rela-
tively high dose of triamcinolone injected into the eye. In all preceding studies at other centers applying intra-
vitreal triamcinolone acetonide for the treatment of exu-
dative age-related macular degeneration or other macu-
lar diseases, a dose of 4 mg was used.8-12,15-17 The reason we used 25 mg of triamcinolone acetonide was that since the beginning of our ongoing investigations, now invol-
volving more than 400 patients with various diseases, we have used the same dose of 25 mg of triamcinolone acetonide and have not yet seen adverse effects that may be attrib-
uted to that dose. An additional reason to use the high
dose for this study was that in preceding studies on the intravitreal use of 4 mg of triamcinolone acetonide for patients with exudative age-related macular degeneration, the therapeutic effect has not been clear. This es-
pecially holds true for the prospective randomized study performed by Gillies et al17 on the intravitreal use of 4
mg of triamcinolone acetonide for the treatment of exu-
dative age-related macular degeneration.

In several preceding studies, a single intravitreal in-
jection of triamcinolone had already been used as treat-
ment for exudative age-related macular degeneration. In 1998, Challa et al10 evaluated the safety and efficacy of intravitreal triamcinolone after 18 months of follow-up in patients with exudative age-related macular degene-
ration who were considered unsuitable for laser pho-
tocoagulation. In that nonrandomized clinical pilot study, 30 eyes of 28 patients were treated with an intravitreal injection of triamcinolone acetonide (4 mg). Of the 20
eyes with an initial visual acuity of 0.10 or better, vision
was maintained in 11 eyes (55%), whereas 6 eyes (30%) had severe visual loss (≥6 Snellen lines). Visual acuity improved in 3 of 10 eyes with an initial acuity of 20/400 or worse. The authors concluded that a single intravitreal injection of 4 mg of triamcinolone acetonide is reasonably well tolerated and may be helpful in the treatment of exudative age-related macular degeneration. In a randomized clinical trial, Danis et al.\textsuperscript{11} examined the effects of an intravitreal injection of 4 mg of triamcinolone acetonide on the visual and clinical course of exudative age-related macular degeneration in 27 patients who were compared with a nontreated control group. The authors found that visual acuity was significantly (P < .005) better in the treated group compared with control subjects at 3 and 6 months of follow-up. Intraocular pressure elevation was seen in 25% of treated patients but was controlled with topical medications. Progression of cataract was more frequently detected in the treated group. The authors concluded that intravitreal triamcinolone may lead to improvement in visual acuity in exudative age-related macular degeneration.

The results of both our study and the other investigations described are partially in contrast to a recent study by Gillies et al.,\textsuperscript{17} who found no effect of 4 mg of intravitreal triamcinolone acetonide on the development of severe visual loss during a follow-up period of 1 year. Their treated group had more cataract, so a progressive opacification of the lens, reducing visual acuity, may have hidden the positive effect of triamcinolone. One reason for the discrepancy between the investigation by Gillies and colleagues and our study may be the difference in dose of triamcinolone. Another reason may be that injections were not performed in the study by Gillies and colleagues. Their results fit with ours in that the peak in visual acuity occurred about 2 to 5 months after the injection. At the end of their follow-up, the visual acuity was no longer better than prior to the intravitreal injection. Interestingly, Gillies and colleagues found a statistically significant and therapeutically positive effect of intravitreal triamcinolone on the size of subfoveal neovascularization 3 months after the injection. Their study is in agreement with experimental studies regarding an angiostatic effect of intravitreal cortisone on subretinal neovascularization and other types of intraocular blood vessel proliferation.\textsuperscript{5,6} An additional reason for the discrepancy between the study by Gillies and colleagues and ours as well as the preceding studies may be that their investigation included patients with the classic type of subfoveal neovascularization, which is associated with a worse prognosis compared with occult subfoveal neovascularization.

The main adverse effect of intravitreal triamcinolone observed in this study was elevation in intraocular pressure. However, maximal intraocular pressure measurements were lower, but not significantly (P = .55), after the second intravitreal injection than after the first. Only 1 eye that showed elevated intraocular pressure after the second injection had normal intraocular pressure measurements after the first injection. One may infer that if the intraocular pressure remains in the normal range after a preceding intravitreal injection of 25 mg of triamcinolone acetonide, an elevation in intraocular pressure after a second injection is not probable. Future study may reveal whether a steroid-induced increase in intraocular pressure is less marked after a second injection than after the first. With respect to other adverse effects, one may infer that the repeated intravitreal injection did not markedly damage the intraocular tissues; visual acuity did not decrease after the reinjection but increased significantly. Further indication for the tolerability of the second intravitreal injection of 25 mg of triamcinolone acetonide was that the eyes did not show other signs of intraocular toxicity, such as intraocular inflammation or bullous keratopathy due to corneal endothelial dysfunction.

In conclusion, our data suggest that the repeated intravitreal injection of 25 mg of triamcinolone acetonide for the treatment of exudative age-related macular degeneration is associated with a reincrease in visual acuity in patients who, as triamcinolone responders, had shown an improvement in visual acuity after a preceding intravitreal injection of 25 mg of triamcinolone acetonide. The peak in visual acuity and the peak in intraocular pressure elevation occur about 2 to 5 months after each injection.

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REFERENCES