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 $P = .05$ [log-MAR units]). The peak in visual acuity and, in a chronologically parallel manner, the peak in intraocular 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.


AG-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 intravitreal 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 reruduction 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 ± 0.10 (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 = .92), 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, and afterward the patients were completely draped. An eye speculum was inserted, and paracentesis was carried out to decrease the volume of the eye. The injection of 25 mg (0.2 mL) of crystalline triamcinolone acetonide was performed using a sharp 27-gauge needle through the temporal inferior pars plana 3 to 3.5 mm from the limbus. Then a combination antibiotic ointment (polymyxin B sulfate and neomycin sulfate) 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; Steriflux Pur; 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 refractometry.

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 = .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...
did not show a change in visual acuity. Comparing the last postoperative examination with the preoperative examination, an increase in visual acuity was found in 6 patients (46%), and a decrease in visual acuity was observed in 6 patients (46%). Mean visual acuity prior to the injection and at the end of follow-up prior to the second injection did not vary significantly ($P = .81$).

After the second injection, mean±SD visual acuity increased significantly ($P = .003$) from 0.15±0.14 (median, 0.08; range, 0.01-0.40) to a maximum of 0.23±0.19 (median, 0.25; range, 0.02-0.60) (Figure 2). 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 1.04±0.50 to 0.88±0.48 logMAR units. The increase in visual acuity was marginally statistically significant for the measurements obtained 1 month after the injection ($P = .11$). Comparing the last postoperative examination at the end of follow-up with the preoperative examination, an increase in visual acuity was found in 5 patients (38%), and a decrease in visual acuity was observed in 6 patients (46%). Two (15%) of 13 patients did not show a change in visual acuity. Mean±SD visual acuity prior to the injection and at the end of follow-up did not vary significantly (0.15±0.14 vs 0.16±0.16; $P = .89$).

In the control group, mean±SD visual acuity at baseline (0.17±0.10 [range, 0.03-0.30]; median, 0.18) and best visual acuity during follow-up (0.17±0.12 [range, 0.03-0.50]; median, 0.14) did not vary significantly ($P = .81$). Comparing the last examination at the end of follow-up with the baseline examination, an increase in visual acuity was found in 5 patients (38%), and a decrease in visual acuity was observed in 6 (46%). Mean±SD visual acuity was significantly worse at the end of follow-up than at baseline (0.12±0.10 vs 0.17±0.10; $P = .008$). The differences in change in best visual acuity between the study and control groups, expressed in Snellen lines and logMAR units, were significant ($P = .01$ and $P = .05$, respectively). Correspondingly, the number of patients showing an increase in visual acuity by more than 1 Snellen line during follow-up was significantly higher in the study group than in the control group ($P = .005$; $\chi^2$ test).

After the first injection, mean±SD intraocular pressure increased significantly ($P = .009$; Wilcoxon rank sum test) from 14.7±3.0 mm Hg (range, 10-20 mm Hg; median, 15 mm Hg) to a maximum of 20.2±5.3 mm Hg (range, 15-30 mm Hg; median, 18 mm Hg) during follow-up. The difference between the intraocular pressure measurements prior to the injection and at the examination 4 months after the injection was marginally significant ($P = .06$). Four (31%) of 13 eyes developed maximal intraocular pressure measurements higher than 21 mm Hg. In these patients, intraocular pressure could be normalized by topical antiglaucoma treatment. All other patients had postoperative intraocular pressure measurements in the normal range.

After the second injection, mean±SD intraocular pressure increased significantly ($P = .02$; Wilcoxon rank sum test) from 16.1±3.6 mm Hg (range, 12-23 mm Hg; median, 15 mm Hg) prior to the second injection to a maximum of 19.0±5.0 mm Hg (range, 13-28 mm Hg; median, 18 mm Hg) during follow-up. The differences between the intraocular pressure measurements prior to the injection and at the single examinations performed during follow-up were not statistically significant ($P > .10$). The increase in intraocular pressure was most marked for the examinations 3 and 5 months after the reinjection of triamcinolone. Three eyes (23%) developed maximal intraocular pressure measurements higher than 21 mm Hg. For 2 of the 3 eyes, intraocular pressure could be normalized by topical antiglaucoma treatment. One eye had to undergo filtering surgery because progressive glucomatous damage of the optic nerve developed, with intraocular pressure measurements of 30 mm Hg that could not be normalized with topical medication.

Two (67%) of the 3 eyes in which intraocular pressure increased after the second intravitreal injection had also shown an elevation in intraocular pressure after the first intravitreal injection. The third eye in which the maximal intraocular pressure was higher than 21 mm Hg after the second intravitreal injection had had normal intraocular pressure measurements after the first injection. For this eye, only 1 measurement after the second injection was higher than 21 mm Hg. Two (50%) of the 4 eyes that had developed secondary ocular hypertension after the first intravitreal injection had normal intraocular pressure measurements after the second injection.

The frequency of intraocular pressure elevation and the amount of increase in intraocular pressure were statistically independent ($P > .50$) of the increase in visual acuity. For all patients in the study group, the maximal intraocular pressure was lower, but not significantly ($P = .55$), after the second intravitreal injection than the first (mean±SD, 19.0±5.0 mm Hg vs 20.2±5.3 mm Hg).

**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, photodynamic therapy has been less successful for the treatment of occult subfoveal neovascularization.\textsuperscript{3} As an alternative to laser treatment, Penfold et al\textsuperscript{8,9} and Challa et al\textsuperscript{10} started to inject triamcinolone intravitreally in an effort to treat exudative age-related macular degeneration. Similarly to Challa and colleagues, Danis et al\textsuperscript{11} performed a comparative study and reported a beneficial effect of triamcinolone in the study group compared with the control group. Additionally, Ranson et al\textsuperscript{12} applied intravitreal triamcinolone for the treatment of recurring subfoveal choroidal neovascularization after laser treatment. A recent investigation including 71 eyes with exudative age-related macular degeneration demonstrated a significant increase in visual acuity after an intravitreal injection of 25 mg of triamcinolone acetonide. The improvement in visual acuity was significant for the examinations performed 1 month (\(P = .04\)) and 2 months (\(P = .04\)) after the injection. About 3 to 5 months after the injection, visual acuity declined so that measurements obtained at the end of the follow-up period for that study did not differ significantly (\(P = .17\)) from the baseline values. Overall, however, 48 eyes (66.2\%) had gains in visual acuity during the follow-up period.

In our study, patients were re-treated with an intravitreal injection of 25 mg of triamcinolone acetonide if the first intravitreal injection was associated with stabilization or increase in visual acuity. The results suggest that the reinjection led to a significant (\(P = .003\)) improvement in visual acuity, with 10 (77\%) of 13 patients showing an increase in visual acuity during the follow-up period. 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 reinjection if the visual acuity deteriorates again. Our findings 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 demonstrated a reincrease in visual acuity.\textsuperscript{13}

Interestingly, the peak of the increase in visual acuity 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 suggests that a reinjection of triamcinolone may be performed about 3 to 5 months or more after an initial injection 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 intravitreal injection of triamcinolone, patients must undergo close follow-up for several months to detect a steroid-induced increase in intraocular pressure. Besides the chronological correlation between an increase in visual acuity and an elevation in intraocular pressure, the postinjection increase in visual acuity was statistically independent of the elevation in intraocular pressure.

There are limitations to this study. The number of patients treated was relatively small; however, the postinjection visual acuity measurements were significantly better than the baseline values when all patients with an intravitreal reinjection were included. Thus, the small number of patients may support our conclusions. Another important limitation of the study is its design as a nonrandomized comparative investigation. Because the first intravitreal injection of triamcinolone was associated with an increase in visual acuity, it was difficult to convince patients to take part in a randomized trial in which some of them might not receive treatment. Furthermore, comparing the patients in the study group with those in the control group showed significant differences in the change in visual acuity during follow-up. This suggests that the reincrease in visual acuity after the second injection of triamcinolone was caused by the treatment 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,\textsuperscript{14} visual acuity was determined using Snellen charts in a standardized fashion by an observer performing best-corrected refractionometry. However, the same method for assessment of visual 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 cataract, 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 limitation of the study may support its conclusion.

An additional limitation of our study may be the relatively high dose of triamcinolone injected into the eye. In all preceding studies at other centers applying intravitreal triamcinolone acetonide for the treatment of exudative age-related macular degeneration or other macular diseases, a dose of 4 mg was used.\textsuperscript{8,12,15-17} The reason we used 25 mg of triamcinolone acetonide was that since the beginning of our ongoing investigations, now involving 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 attributed 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 especially holds true for the prospective randomized study performed by Gillies et al\textsuperscript{17} on the intravitreal use of 4 mg of triamcinolone acetonide for the treatment of exudative age-related macular degeneration.

In several preceding studies, a single intravitreal injection of triamcinolone had already been used as treatment for exudative age-related macular degeneration. In 1998, Challa et al\textsuperscript{12} evaluated the safety and efficacy of intravitreal triamcinolone after 18 months of follow-up in patients with exudative age-related macular degeneration who were considered unsuitable for laser photocoagulation. 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 al11 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.17 who found no effect 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 concluded that visual acuity was no longer better than prior to the intravitreal injection. Interestingly, Gillies and colleagues found that visual acuity was significantly higher in the treated eyes than in the control eyes at 3 and 6 months after the injection. The authors concluded that intravitreal triamcinolone may lead to improvement in visual acuity in exudative age-related macular degeneration.

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 reincreased 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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