European Journal of Ophthalmology / Vol. 15 no. 6, 2005 / pp. 751-758

# Intravitreal triamcinolone acetonide for treatment of central retinal vein occlusion

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PURPOSE. *To evaluate the effect of intravitreal triamcinolone acetonide on visual acuity and intraocular pressure in patients with central retinal vein occlusion.*
METHODS. *This prospective comparative non-randomized clinical interventional study included 32 patients (33 eyes) with central retinal vein occlusion. The study group (12 patients; 13 eyes) received an intravitreal injection of about 20 mg of triamcinolone acetonide. The control group (20 patients) did not receive any treatment. Mean follow-up was 10.1±8.6 months in the study group and 6.0±5.2 months in the control group.*
RESULTS. *In the study group, mean visual acuity increased significantly (p=0.018) from 0.11±0.11 preoperatively to a best visual acuity during follow-up of 0.18±0.15. An improvement in visual acuity by at least 2 Snellen lines and 3 Snellen lines, respectively, was found for 8 (62%) eyes and 5 (38) eyes. Visual acuity measurements determined 1 month (p=0.038) and 3 months (p=0.046) after the injection were significantly higher than the baseline values. Increase in visual acuity was higher in the non-ischemic subgroup than in the ischemic subgroup. In the control group, baseline visual acuity and best visual acuity during the follow-up did not vary significantly (p=0.33). Visual acuity decreased significantly (p=0.007) towards the end of the follow-up. Comparing study group and control group, gain in visual acuity was significantly (p=0.01) higher in the study group. In the study group, intraocular pressure increased significantly (p=0.018) from 14.4±3.9 mmHg to a mean maximal value of 21.6±9.2 mmHg (range, 10–44 mmHg), and re-decreased (p=0.012) towards the end of follow-up to 15.3±5.1 mmHg (range, 10–21 mmHg).*
CONCLUSIONS. *Intravitreal triamcinolone acetonide temporarily increases visual acuity in central retinal vein occlusion. It is accompanied by an increase in intraocular pressure. (Eur J Ophthalmol 2005; 15: 751-8)*

KEY WORDS. *Central retinal vein occlusion, Cystoid macular edema, Intraocular pressure, Intravitreal triamcinolone, Iris neovascularization, Secondary angle-closure glaucoma, Steroid response*

*Accepted:* June 13, 2005

## INTRODUCTION

Cystoid macular edema is one of the major causes of decreased vision in patients with central retinal vein occlusion. With the exception of retinal laser coagulation in eyes with early iris neovascularization, other therapeutic options have not been proven effective to increase visual acuity after central retinal vein occlusion (1-3). For decades, corticosteroids have been known to reduce inflammation and tissue edema. Given topically or systemically, however, corticosteroids have not been shown to be helpful in the treatment of central retinal vein occlusion.

 1120-6721/751-08$15.00/0

Since recent studies suggested that intravitreal triamcinolone acetonide, which is a crystalline corticosteroid, can reduce cystoid macular edema caused by various reasons (4-13), we evaluated whether intravitreal triamcinolone acetonide is useful for the treatment of cystoid macular edema due to central retinal vein occlusion.

## PATIENTS AND METHODS

This prospective comparative non-randomized clinical interventional study included 33 eyes of 32 patients with central retinal vein occlusion. The whole study population was divided into a study group consisting of 13 eyes of 12 patients, who received an intravitreal injection of about 20 mg of triamcinolone acetonide, and a control group including 20 eyes of 20 patients who did not receive any treatment of central retinal vein occlusion during the study period. Study group and control group did not vary significantly in age (p=0.32), preoperative intraocular pressure (p=0.25), refractive error (p=0.32), or sex (p=0.44) (Tab. I). All patients underwent fluorescein angiography at baseline of the study. During follow-up, fluorescein angiography was not performed in a regular scheme for all patients included in the study.

Differentiating between an ischemic type versus non-ischemic type of central retinal vein occlusion revealed that in the study group, 4 (31%) eyes showed the ischemic type, and in the control group, 5 (25%) eyes showed the ischemic type. Study group and control group did not vary significantly (p=0.51, chi-square test) in the proportion of the ischemic type versus non-ischemic type of the central retinal vein occlusion. All patients receiving the intravitreal injection were fully informed about the experimental character of the treatment and signed an informed consent. The ethics committee of the University had approved the study, which followed the tenets of the Declaration of Helsinki. For one patient in the study group presenting with bilateral central retinal vein occlusion, both eyes received an intravitreal injection of triamcinolone, with a time interval of 10 weeks between the two injections. The decision to offer the patients a treatment with intravitreal triamcinolone acetonide depended on several factors, one of which was the ophthalmologist seeing the patients at the study site. Some ophthalmologists usually offered the treatment while other ophthalmologists in the department usually did not discuss the therapy. The period when the patients came to the hospital was another factor influencing the decision of assigning the patients to the study group or control group with more patients assigned to the control group in the early phase of the study. Another reason for assigning the patients to the study group or the control group was that the patients of the control group did not want to get an intravitreal injection, which has been considered to be an experimental clinical procedure. Mean follow-up was 10.1±8.6 months (range, 1.1–22.7 months) in the study group and 6.0±5.2 months (range, 1.1–19.3 months) in the control group with no significant (p=0.41) difference between the groups (Tab. I).

Fluorescein angiogram performed at baseline of the study showed a marked cystoid macular edema, in addition to marked intraretinal hemorrhages. All patients complained about a loss of vision experienced at least 3 months prior to the intravitreal injection. At baseline of the study and in repeated intervals afterwards, all patients underwent a routine ophthalmologic examination including standardized visual acuity measurement using Snellen charts, slit lamp biomicroscopy, Goldmann applanation tonometry, and ophthalmoscopy. In the study group, the examinations were performed during the first week after the injection, and roughly in monthly or bimonthly intervals after the injection. According to the fluorescein angiogram, 6 (46%) patients of the study group and 3 (20%) of the control group showed the ischemic type of central retinal vein occlusion.

The intravitreal injection of triamcinolone acetonide was performed under sterile conditions in the operation theatre using an operation microscope. Prior to the intravitreal injection, topical Betadine (povidone-iodine 5%) (Alcon, Ft Worth, TX) was applied, and after that the patients were completely draped. A lid speculum was inserted and a paracentesis carried out to decrease the volume of the eye. The injection of 20 to 25 mg (0.2 mL) crystalline triamcinolone acetonide was performed through a sharp 27-gauge needle through the inferior pars plana, at 3 mm to 3.5 mm from the limbus. After that, an antibiotic ointment (polymyxin and neomycin) was applied. The triamcinolone acetonide had been prepared by extracting 0.625 mL from the ampoule (Volon A, Bristol-Myers-Squibb, Germany) containing 40 mg of triamcinolone acetonide in 1 mL. The extracted volume was filled into a tuberculin syringe (1 mL) or a 2 mL syringe. The syringe was filled up with Ringer's solution. A Millipore filter (pore size, 5 micrometers) was placed on top of the syringe, and most of the content of the syringe was pressed through the filter, with the triamcinolone acetonide crystals remaining in the

syringe. The syringe was re-filled with Ringer's solution, and the same procedure was repeated three times. At the end, 0.2 mL of solution in the syringe were left, and using a 27-gauge needle, the content was injected transconjunctivally into the vitreous cavity.

Statistical analyses were performed by using a commercially available statistical software package (SPSS for Windows, version 11.5, SPSS, Chicago, IL). To test the statistical significance of differences between the study group and the control group, the Mann-Whitney test, Wilcoxon test, or Student t-test for parameters such as intraocular pressure and visual acuity were used. For parameters such as sex and right or left eye, the chi-square test was applied. The level of significance was 0.05 (two-sided) in all statistical testing.

## RESULTS

In the study group, mean visual acuity increased significantly (p=0.018) from 0.11±0.11 (1.20±0.55 logMar units) preoperatively to a best visual acuity during the follow-up of 0.18±0.15 (0.96±0.57 logMar units) (Tab. II). Ten (77%) eyes showed at least one visual acuity measurement which was better during the follow-up compared with the baseline of the study.

An improvement in visual acuity by at least 2 Snellen lines was found for 8 (62%) eyes, and 5 (38%) eyes showed an improvement of 3 or more Snellen lines. Visual acuity measurements determined 1 month (p=0.038) and 3 months (p=0.046) after the injection were significantly higher than the baseline values. Visual acuity measurements returned to the baseline level about 5 months after the injection. Considering visual acuity measurements taken at the end of the follow-up, the difference to the baseline visual acuity was not significant (p=0.42).

Dividing the study group into the ischemic subgroup (n=4) and the nonischemic group (n=9) revealed that preoperative visual acuity was significantly (p=0.003) higher in the non-ischemic subgroup (0.15±0.12 [0.93±0.32 logMar units] versus 0.02±0.02 [1.79±0.51 logMar units]). In the non-ischemic subgroup, visual acuity increased significantly (p=0.04) from baseline to best postoperative visual acuity (0.15±0.12 to 0.24±0.14 [0.69±0.25 logMar units]; p=0.04). In the ischemic subgroup, visual acuity did not vary significantly (p=0.10) between baseline value and best postoperative visual acuity (0.02±0.02 to 0.04±0.03 [1.57±0.64 logMar units]; p=0.10).

In the control group, baseline visual acuity and best visual acuity during the follow-up did not vary significantly (0.32±0.27 [0.64±0.38 logMar] versus 0.32±0.22 [0.63±0.34 logMar]; p=0.33).

**TABLE I -** COMPOSITION OF THE STUDY POPULATION AND VISUAL ACUITY PRIOR TO THE INTRAVITREAL INJECTION OF 25 MG TRIAMCINOLONE ACETONIDE

| | **Study group** | **Control group** | **p value** |
|---|---|---|---|
| No. | 13 | 20 | |
| Age, y | 70.0±12.8 | 63.7±12.5 | 0.32 (NS) |
| Median | 70.3 | 66.1 | |
| Range | 50.7–95.1 | 38.6–79.6 | |
| Female/male | 4/8 | 8/12 | 0.44 (NS) |
| Right eye/left eye | 7/6 | 11/9 | 0.61 (NS) |
| Refract. error | 1.18±2.04 | 0.26±2.25 | 0.32 (NS) |
| Median | 0.75 | 0.25 | |
| Range | -0.75 to +5.50 | -5.0 to +5.75 | |
| Follow-up period, months | 10.1±8.6 | 6.0±5.2 | 0.41 (NS) |
| Median | 6.9 | 4.1 | |
| Range | 1.1–22.7 | 1.1–19.3 | |
| Intraocular pressure, mmHg | 14.4±3.9 | 13.9±2.9 | 0.25 (NS) |
| Median | 15 | 14 | |
| Range | 10–19 | 9–21 | |

p value= Significance of difference between preoperative visual acuity and postoperative visual acuity in each study group

Visual acuity decreased significantly (p=0.008) towards the end of the follow-up (0.27±0.27 [0.74±0.40 logMar]). Best visual acuity during follow-up was higher than baseline visual acuity in 7 (35%) patients, and it was lower in 9 (45%) patients. Comparing study group and control group with each other, gain in best visual acuity during follow-up was significantly (p=0.010) higher in the study group. Correspondingly, gain in visual acuity was significantly higher in the study group than in the control group for the measurement obtained at 1 month (p=0.003) after inclusion into the study.

In the study group, intraocular pressure increased significantly (p=0.018) from 14.4±3.9 mmHg at baseline of the study to a mean maximal value of 21.6±9.2 mmHg (median 20 mmHg; range, 10–44 mmHg). Towards the end of the follow-up, intraocular pressure decreased again (p=0.012) to 15.3±5.1 mmHg (median, 17 mmHg; range, 10–21 mmHg). Preoperative intraocular pressure measurements and the measurements at the end of the follow-up did not differ significantly (p=0.87). During the study period, intraocular pressure was higher than 21 mmHg in 3 (23%) eyes. In all of these eyes, intraocular pressure could be normalized by topical antiglaucomatous medication.

In the control group, intraocular pressure during the follow-up (peak: 16.3±3.9 mmHg; range, 12–28 mmHg) was slightly (p=0.01) higher than at baseline of the study (13.9±2.9 mmHg) and at the end of the study (15.2±3.1 mmHg, p=0.06). Two (20%) eyes of the control group developed intraocular pressure measurements higher than 21 mmHg during the follow-up. Intraocular pressure during the follow-up was significantly (p=0.007) higher in the study group than in the control group. Neither group varied significantly in intraocular pressure at baseline of the study (p=0.25) and at the end of follow-up (p=0.65).

Postoperative infectious endophthalmitis, postoperative sterile endophthalmitis, pseudo-endophthalmitis, rhegmatogenous retinal detachment, or proliferative vitreoretinopathy did not occur in any of the eyes included in the study. Triamcinolone acetonide crystals did not settle on the macular region. The crystals were preretinally located in the vitreous cortex at the 6 o'clock position and did not optically interfere with vision.

## DISCUSSION

Based on experimental and clinical investigations by Machemer, Peyman, and other researchers, recent studies have suggested that intravitreal triamcinolone acetonide may be a therapeutic option for several intraocular diseases exhibiting macular edema and intraocular neovascularization. These diseases include diabetic macular edema (3-5), exudative age-related macular degeneration (14-19), proliferative diabetic retinopathy (20), neovascular glaucoma (21, 22), proliferative vitreoretinopathy (23, 24), chronic pre-phthisical ocular hypotony (25), chronic uveitis (6-8, 26), persistent pseudophakic cystoid macular edema (9-11), and other clinical conditions (27-29). Recently, the clinical courses of patients receiving an intrav-

**TABLE II -** VISUAL ACUITY IN THE STUDY GROUP

| | **Visual acuity (Snellen lines)** | **p value** | **Gain in visual acuity** |
|---|---|---|---|
| Preoperative | 0.11±0.11 (n=13) | | |
| Postinjection | | | |
| 1 wk | 0.12±0.08 (n=8) | 0.23 (NS) | 1.6±1.8 |
| 1 mo | 0.14±0.15 (n=11) | 0.038 | 1.7±2.1 |
| 2 mo | 0.15±0.14 (n=5) | 0.29(NS) | 1.4±2.5 |
| 3 mo | 0.11±0.07 (n=7) | 0.046 | 2.1±2.3 |
| 4 mo | 0.17±0.16 (n=5) | 0.29 (NS) | 1.8±4.1 |
| 5 mo | 0.18±0.11 (n=2) | 0.32 (NS) | 2.0±2.8 |
| 6 mo | 0.09±0.06 (n=5) | 0.47 (NS) | -0.4±3.4 |
| 7 mo | 0.12±0.07 (n=5) | 0.50 (NS) | -1.2±2.6 |
| 8 mo | 0.08±0.07 (n=3) | 1.00 (NS) | 0.3±4.2 |
| Best postop. visual acuity | 0.18±0.15 (n=13) | 0.020 | 2.4±2.6 |
| Visual acuity at study end | 0.08±0.06 (n=13) | 0.42 (NS) | -0.8 ±3.3 |

p value= Significance of difference from the baseline visual acuity.

itreal injection of triamcinolone acetonide as a treatment trial for macular edema due to central retinal vein occlusion have been reported (30-36). In these studies, the intravitreal application of crystalline cortisone resulted in a decrease of cystoid macular edema and an increase in visual acuity.

These reports are in agreement with the present comparative investigation. The intravitreal injection of triamcinolone resulted in a statistically significant increase in mean visual acuity in the study group. The rise in visual acuity was significantly higher in the study group than in the control group in which visual acuity did not increase during the follow-up. The difference between the present study and the preceding studies on the intravitreal use of triamcinolone acetonide as treatment of central retinal vein occlusion is that the previous studies were mostly case reports or case series studies in contrast to the present investigation with a comparative non-randomized study design. The results of the present study agree with observations made in other investigations in which intravitreal triamcinolone acetonide reduced macular edema caused by other reasons than central retinal vein occlusion (3-11).

The results of the present study additionally suggest that the increase in visual acuity after the intravitreal injection of triamcinolone acetonide may not last permanently in eyes with central retinal vein occlusion. After a significant increase in visual acuity in the first 3 months after the injection, visual acuity showed a tendency of a decline towards the end of the study. Correspondingly, final visual acuity and preoperative visual acuity did not vary significantly. This is similar to a previous study on patients with exudative age-related macular degeneration who repeatedly received intravitreal injections of about 20 mg of triamcinolone acetonide and who repeatedly showed an increase in visual acuity lasting up to 5 months after each injection (37). Future studies may address the question whether repeated intravitreal injections or intravitreal slow-release devices such as described by Jaffe et al may overcome the problem of a temporary effect of an intravitreal triamcinolone acetonide injection (38).

The finding of the previous investigations (30-36) and the present study that the intravitreal application of triamcinolone acetonide may be useful to decrease macular edema in patients with central retinal vein occlusion may be clinically interesting since no proved treatment exists for macular edema secondary to central retinal vein occlusion (2). Generally, macular edema due to central retinal vein occlusion carries a poor visual prognosis. After 3 years, 58% of eyes will have vision worse than 20/100. Less than 20% of eyes will gain two or more lines of visual acuity. In addition, there are no proved treatment options. Correspondingly, the Central Vein Occlusion Study demonstrated that grid photocoagulation had no significant impact on the final visual acuity of eyes with central retinal vein occlusion and macular edema (2).

The reasons why intravitreal steroids increase vision in patients with macular edema due to central retinal vein occlusion or due to other edematous macular diseases have been elusive; however, stabilization of the blood-retinal barrier may play a significant part (39, 40). One of the reasons why visual acuity did not increase more than reported in the previous case reports and the present study may be macular ischemia and tissue destruction accompanying central retinal vein occlusion. It may be the reason for a discrepancy between morphologic improvement as demonstrated by a decrease in the leakage of fluorescein and thinning of the macula, and only a slight increase in visual acuity. It supports the hypothesis that intravitreal triamcinolone acetonide improves visual acuity as much as macular ischemia and tissue destruction allow it.

Direct toxic effects of triamcinolone acetonide on the retina and optic nerve were not observed in the present study nor in other studies on eyes in which the same dosage of triamcinolone acetonide was injected for various reasons (4, 6, 12, 18-26). Correspondingly, a recent safety and efficacy study of an intravitreal fluocinolone acetonide sustained delivery device as treatment for cystoid macular edema in patients with uveitis (38) and other clinical and experimental studies have not shown a toxic effect of intraocular steroids (8, 41-44). An elevation of intraocular pressure above 21 mmHg occurring in 4 eyes (31%) in the present study was not a major clinical problem. In all these eyes, intraocular pressure could be controlled by topical antiglaucomatous treatment. Similar observations were made by Wingate et al (16) and Martidis et al (4) using a dosage of 4 mg of triamcinolone acetonide, as well as in other previous studies using a dosage of about 20 mg of triamcinolone acetonide (45). The results are partially contradictory to those obtained by Kaushik et al (34).

A major difference between the studies on the intravitreal application of triamcinolone acetonide performed by others and the present investigation is the dosage of triamcinolone intravitreally injected. In all previous studies on intravitreal applications of triamcinolone acetonide for

cystoid macular edema, diabetic macular edema, and macular degeneration performed by other researchers, dosages of 4 mg or less of triamcinolone acetonide were used. Reasons why we used a dosage of about 20 mg of triamcinolone acetonide instead of a dosage of 4 mg have been that right from the beginning of the ongoing triamcinolone studies now involving more than 900 intravitreal injections, we have used the same dosage of about 20 mg of triamcinolone acetonide, and that a recent randomized study suggested that the duration of the effect of intravitreal triamcinolone acetonide depends on the dosage used (46).

The most important limitation of the present study is that it is not a randomized prospective investigation in which the patients were randomly distributed between the study group and the control group. It may also be the reason why the follow-up was shorter in the control group than in the study group. Yet 10 (77%) of eyes gained in visual acuity after the injection of triamcinolone acetonide, with 8 (62%) eyes gaining in visual acuity by at least two Snellen lines or more. This result may be better than the natural course of the disease as suggested in the control group of the present investigation as well as by previous studies (2). Furthermore, one has to consider that the effect of a triamcinolone induced cataract formation on visual acuity has not been taken into account in the assessment of visual acuity in the present study. The cataract associated decrease in visual acuity may have compensated or partially covered an increase in visual acuity due to the effect of triamcinolone acetonide. Another limiting factor might be the relatively small number of patients included in the study. Despite the relatively small number of patients, however, the post-injection visual acuity was significantly better for the study group than for the control group, and increased visual acuity within the study group during the follow-up. The small number of patients might thus support the conclusion of the study. Another limitation may be that the observer was not masked and usually knew that the patient had received an intravitreal injection of triamcinolone acetonide. Another limitation of the study is that Snellen acuity charts were used instead of charts as used in the Early Treatment of Diabetic Retinopathy Study (ETDRS). This limitation accounts, however, for the study group as well as the control group, and may, therefore, not have markedly influenced the conclusions of the study. An additional limitation of the study may be that optical coherence tomography was not used as an additional diagnostic tool. Many but not all patients underwent optical coherence tomography at baseline of the study, and the majority but not all patients underwent optical coherence tomography during follow-up in regular intervals. Although optical coherence tomographic data would have added valuable information to the study, the available data were not included into the study, since the data were not sufficient to compare study group and control group, or to show the change in macular thickness during follow-up within the groups. There was the clinical impression that most eyes of the study group showed a decrease in macular thickness in optical coherence tomography, and that the eyes of the control group did not vary markedly in macular thickness during follow-up. The increase in visual acuity in the eyes of the study group was additionally and negatively dependent on the amount of macular ischemia. All this information is, however, anecdotal, and is not based on solid scientific data.

In conclusion, 1 to 3 months after the intravitreal injection of about 20 mg of triamcinolone acetonide patients with central retinal vein occlusion showed a slight but statistically significant increase in visual acuity. Towards the end of the study, visual acuity tended to decrease again to the baseline values. The patients of the study group performed significantly better than the patients of a nonrandomized control group. Side effects of the intravitreal injection of triamcinolone acetonide were an elevation in intraocular pressure in 3 (23%) eyes, which could be controlled medically. In agreement with previous studies on the effect of intravitreal triamcinolone acetonide on macular edema due to central retinal vein occlusions (29-35), the results of the present study suggest that the intravitreal injection of triamcinolone acetonide may be a therapeutic option to temporarily increase visual acuity in patients with central retinal vein occlusion.

*The authors have no proprietary interest in any aspect of the article.*

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