Treatment of Cystoid Macular Edema in Retinitis Pigmentosa With Intravitreal Triamcinolone

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Objective: To evaluate the results of treatment with intravitreal triamcinolone acetonide injection in patients with cystoid macular edema secondary to retinitis pigmentosa.

Methods: This prospective, nonrandomized comparative trial included 20 eyes of 20 patients with cystoid macular edema secondary to retinitis pigmentosa (group A) and 20 eyes of 20 control individuals (group B) with the same characteristics who declined treatment. All treated eyes received an intravitreal injection of 0.1 mL of triamcinolone acetonide (4 mg). The total follow-up was 12 months. The main outcome measures were best-corrected visual acuity, central macular thickness measured by optical coherence tomography, and intraocular pressure.

Results: No statistically significant changes were observed in best-corrected visual acuity. Central macular thickness showed statistical differences between the 2 groups. Intraocular pressure showed a statistically significant increase after the first day, at 1 month, and at 3 months in both groups but no significant increase afterward.

Conclusions: Intravitreal triamcinolone administration may be useful for select cases of cystoid macular edema in patients with retinitis pigmentosa but its efficacy seems to be limited over time. Therefore, to obtain a good anatomical result and an improvement of best-corrected visual acuity, further treatment would be necessary after 6 months.

Arch Ophthalmol. 2007;125:759-764

Retinitis pigmentosa (RP) is a hereditary condition with an incidence in Italy of 1 in 4000. It is very heterogeneous, both phenotypically and genetically. No effective approach for prevention, stabilization, or reversal exists for the majority of RP cases. More than 70 different genetic defects (27 identified genes) have been identified including autosomal recessive (16%), autosomal dominant (22%), and X-linked (9%), with the remaining cases being simplex (with no known inheritance pattern). Actually, many in the simplex RP group are likely to have hereditary causes as has been shown in a number of genetic studies (fully 20% of simplex males have X-linked RP, according to several studies).2-4

Retinitis pigmentosa is a degenerative process of the retina primarily affecting the rod photoreceptors and retinal pigment epithelium (RPE). Although the rod photoreceptors appear to be the primary target of the disease, there is histological and functional evidence for cone photoreceptor damage that is likely secondary to the rod degeneration.5-6 In most cases, patients show an early night blindness and loss of peripheral field of vision but central vision is generally preserved until the late stages of the disease.

In spite of this, in RP, different studies have shown a prevalence of cystoid macular edema (CME) of about 10% to 15%, most of these in cases without an inheritance pattern.7 This complication leads to a reduced visual acuity in such patients. Different therapies have been proposed to resolve CME, such as laser photocoagulation; vitreoretinal surgery, including pars plana vitrectomy associated with posterior hyaloid dissection; removal of the posterior inner limiting membrane and gas tamponade; carbonic anhydrase inhibitors; and systemic corticosteroids. According to previous studies, the most effective therapies seem to be acetazolamide and corticosteroids.8-12

Intravitreal triamcinolone acetonide has already been used in different retinal pathological conditions complicated by CME in their clinical development.13 The purpose of our study was to evaluate the anatomical and visual results of treatment with intravitreal triamcinolone injections in patients with CME secondary to RP.
Our prospective study included 20 eyes of 20 patients with CME secondary to RP (12 men, 8 women) ranging in age from 28 to 54 years (mean ± SD age, 40.2 ± 13 years) (group A). Patients were randomly selected from the Retinitis Pigmentosa Association, which is related to the Low Vision Centre, Department of Pathophysiological Optics, University of Bologna. Institutional review board approval was obtained for the study.

Inclusion criteria, present in all 20 eyes, were presence of ocular findings of RP (perivascular bone spiculelike pigmentation, attenuated retinal arterioles); contracted visual field; non-recordable or markedly reduced a-wave and b-wave amplitudes in the rod and mixed responses on electroretinography; CME documented by contact lens ophthalmoscopy, fluorescein angiography (FA) (all patients had CME with leakage at FA), and optical coherence tomography (OCT), present for 6 months or more (until 18 months); best-corrected visual acuity (BCVA) of 20/200 or better; and ineffective treatment with oral acetazolamide (250 mg of oral acetazolamide twice daily for 1 month) and topical ciprofloxacin eyedrops were used 3 times a day for 1.5 weeks and timolol maleate eyedrops, twice a day for a 3-week period.

A control group (group B) was also selected consisting of 20 eyes of a further 20 patients with CME secondary to RP and a mean ± SD age of 39.5 ± 11.3 years (9 men, 11 women). Group B included patients who had refused surgical treatment (intravitreal injection of triamcinolone).

Evaluation parameters were BCVA of the 2 groups measured using Early Treatment of Diabetic Retinopathy Study and logarithm of the minimum angle of resolution (logMAR) visual acuity charts, central macular thickness measured by Stratus OCT 3 using Retinal Thickness Map Analysis software (Carl Zeiss Meditec, Dublin, Calif) to consider the thickness of the foveal zone, and IOP measured by Goldmann application tonometry at slitlamp. Complications related to intravitreal injection of corticosteroids were recorded. Patients were examined on day 1, after 1 month, and then after 3, 6, and 12 months.

Statistical analysis was performed using SPSS 13.0 for Windows (SPSS Inc, Chicago, Ill). Continuous variables are expressed as mean ± SD; categorical variables are expressed as numbers and percentages. Separate repeated-measures analysis of variance models were used to assess differences between group A and group B patients for the within-subjects effect of modifying BCVA, central macular thickness, and IOP. The Mauchly sphericity test was used to examine the form of covariance matrix; in case of violation of assumption, the Huynh-Feldt correction factor was considered to obtain the adjusted P values for each univariate F test involving the interval effect. Bonferroni correction was used for multiple post hoc comparisons. P values <.05 were considered significant.

### RESULTS

The BCVA results during follow-up are shown in the Table and Figure 1. There was no difference between mean BCVA values for group A and group B patients over time (P=.78), while in general, the mean BCVA values changed significantly from baseline to 12 months (P<.001).

Group A and group B had statistically significant mean central macular thickness values as measured by OCT (P<.001), as shown in the Table and Figure 2. Mean central macular thickness values changed significantly from baseline to 12 months (P<.001). Figure 3 shows the OCT results of a case from before treatment until 18 months after treatment.

### METHODS

Abbreviations: ANOVA, analysis of variance; BCVA, best-corrected visual acuity; CMT, central macular thickness; logMAR, logarithm of the minimum angle of resolution; IOP, intraocular pressure; OCT, optical coherence tomography.

*P value from testing differences between group A and group B in BCVA, CMT, and IOP mean values overall across intervals.

†As measured by OCT.

<table>
<thead>
<tr>
<th>Table. Repeated-Measures ANOVA</th>
<th>Mean ± SD</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA, logMAR (P=.78†)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>0.66 ± 0.21</td>
<td>0.67 ± 0.23</td>
</tr>
<tr>
<td>Group B</td>
<td>0.64 ± 0.20</td>
<td>0.64 ± 0.20</td>
</tr>
<tr>
<td>CMT, µm‡ (P&lt; .001†)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>456 ± 95</td>
<td>302 ± 82</td>
</tr>
<tr>
<td>Group B</td>
<td>444 ± 79</td>
<td>451 ± 78</td>
</tr>
<tr>
<td>IOP, mm Hg (P=.02†)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>14.7 ± 2.2</td>
<td>20.1 ± 5.6</td>
</tr>
<tr>
<td>Group B</td>
<td>15.2 ± 1.7</td>
<td>14.9 ± 1.9</td>
</tr>
</tbody>
</table>

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Ten eyes (50%) developed IOP values of 21 mm Hg or more; of those, 2 eyes (10%) showed an IOP of between 30 and 35 mm Hg. These values were recorded on the first day after treatment with the injection and returned to baseline values 6 months after treatment. The mean IOP values during follow-up are shown in the Table and Figure 4; the 2 groups had statistically different mean values. The pattern of difference between mean IOP values for group A and group B patients changed across intervals. All eyes that showed ocular hypertension (IOP>21 mm Hg) were treated with a topical IOP-lowering medication (0.5% timolol maleate eyedrops twice daily for 1 month) until the IOP returned to its original value.

No injection-related complications were encountered, and no cases of endophthalmitis, postoperative cataract, or acute ocular hypertension were recorded.

The mechanism of CME in patients with RP is not clear. The pathogenesis of CME is probably due to an RPE pumping mechanism reduction, which occurs in cases characterized by later spreading of the FA staining at the level of the RPE in the late transit phases of FA. A dysfunction of anticalcium anhydride and enolase activity by autoantibodies in the RPE may lie at the root of edema formation.

Autoantibodies to enzymes and other important cytoplasmatic and membrane proteins have been found frequently in association with other autoimmune disease, even in first-degree relatives. For example, antipyruvate dehydrogenase antibodies have been detected in insulin-dependent diabetes mellitus and stiff-man syndrome. Another disorder, autoimmune angioedema, is characterized by recurrent episodes of edema and by the presence of autoantibodies that react with C1 inhibitor. It has been shown that the autoantibody binds to C1 inhibitor and facilitates its proteolytic cleavage by specific enzymes.

Autoantibodies to carbonic anhydrase 1 and 2 have been detected in sera of patients with a variety of autoimmune diseases: 30% of patients with systemic lupus erythematosus, polymyositis, and systemic sclerosis; 21% of patients with Sjögren syndrome; and 69% of patients with endometriosis. Only 11.8% of control individuals had antibodies to carbonic anhydrase 2.

Some authors have observed an important relationship between CME in RP and the presence of circulating anti-retinal antibodies. According to these authors, CME in RP is a negative prognostic factor and is associated with an increase of circulating anti-retinal antibodies and with anatomical features that could aggravate visual recovery. These authors suggest an autoimmune process. Heckenlively et al think that a breakdown of the blood-retinal barrier during the retinal degenerative process could release retinal proteins into the circulation that could be antigenic. This can explain how retinal antigens sensitize the immune system and how anti-retinal antibodies can reach the retina when normally the blood-retinal barrier would prevent this option. The presence of anti-retinal antibodies is quite common, with 37% of patients showing indirect immunofluorescent activity. However, it is not known whether anti-retinal antibodies in general or specific ones are harmful and if there are cofactors that may contribute to pathogenicity.

The steroids could exert the effect by several mechanisms, which include reducing levels of proinflammatory cytokines, reducing levels of vascular endothelial growth factor, and increasing blood-retinal barrier function with edema resolution. Intravitreal steroids have an effect on diseases with marked inflammatory composite in their immunopathogenesis. For this reason, we feel they are useful for patients with RP.

Corticosteroids reduce inflammation by suppressing inflammatory cell proliferation and migration and decreasing the synthesis and release of other proinflammatory molecules (prostaglandins and leukotrienes, vascular endothelial growth factor, and intercellular...
adhesion molecule 1).26-29 By intravitreal injection, a large dose of medication is delivered directly to its site of action; this does not occur using alternative ways of administration.30-35

Soluble cortisone is eliminated from the eye within 24 hours after a single intravitreal injection.31 Machemer suggested using a crystalline form of corticosteroid that provides intraocularly available cortisone for a considerably longer period.26,36 Triamcinolone is a crystalline form of steroid that has been reported to be present intracellularly in measurable concentrations up to 1.5 years after intravitreal injection.37

A recent study by Yeung et al38 reported on a possible cytotoxic effect of triamcinolone. They cultured an RPE cell line (ARPE-19) and added corticosteroids (0.01-1 mg/mL) or vehicle (0.025% benzyl alcohol) diluted in culture medium. Subsequently, the culture medium containing corticosteroid or vehicle was refreshed daily. After 1, 3, and 5 days, the proliferated amount of cells with and without corticosteroid treatment was determined. They found that triamcinolone caused a significant reduction in cell numbers throughout the whole range of concentrations when cells were exposed to it for more than 1 day. Compared with dexamethasone sodium phosphate and hydrocortisone, triamcinolone showed the higher relative toxicity.

Another study from Yeung et al39 compared in vitro the cytotoxic effect of triamcinolone on human glial cells (cell line SVG). The study concluded that triamcinolone had cytotoxic effects on both SVG and the RPE, with higher efficacy on SVG. The results suggest that triamcinolone toxic effects on 1 cell type may not reliably indicate its toxic effects on other cells.

Narayanan at al40 performed experiments on R28 (retinal neurosensory cells) and ARPE-19 cells with 1 mg/mL of triamcinolone acetonide and concluded that triamcinolone has toxic effects on proliferating cells of retinal origin in vitro at doses normally used in clinical practice. In in vivo experiments, Bakri and Beer41 showed that preservative-free triamcinolone had no toxic effects on the retina. They used a formulation that did not contain benzyl alcohol as a preservative. In conclusion, benzyl alcohol at concentrations modestly higher than that present in the commercial drug has toxic effects on the eye. It is suggested that if commercial-preserved triamcinolone is to be used clini-
cally, decanting or another means of removing the benzy l alcohol should be considered.

We selected OCT to study macular edema because previous studies showed a similar capacity between OCT and FA in monitoring CME and all the included eyes had CME with leakage at FA at the beginning of the study. Optical coherence tomography could detect cystoid macular lesions in patients with RP even in eyes with either little or no dye accumulation on FA or cystic macular lesions visible by ophthalmoscopy. Stanga et al presented preliminary findings showing that OCT imaging is at least as sensitive as FA for identifying CME and is a useful procedure for evaluating a response to therapy. Moreover, we preferred OCT because of the psychological condition of patients with RP: they refused to undergo FA several times.

In our study, all patients showed an anatomical improvement at 3 months after intravitreal injection of triamcinolone; in terms of visual acuity, 12 of 20 eyes showed an improvement, 4 of 20 remained stable, and 4 of 20 showed worsening. Our results show that the median±SD central macular thickness decreased from 459.89±96.4 µm (range, 310-625 µm) to 306.75±81.8 µm (range, 214-485 µm) at 1 month; 272.78±64.6 µm at 3 months; 302.89±75.7 µm at 6 months; and 442±95.5 (µm range, 325-607 µm) at 12 months, which is similar to the baseline thickness. Our BCVA results, as shown in the Table, were not statistically significant, but some eyes experienced a line gain across time. These results were unexpected based on previous reports of CME in RP that showed an improvement of anatomical resolution and BCVA only at the 1-month follow-up.

Finally, intravitreal triamcinolone administration may be useful for select cases of CME in patients with RP, but its efficacy seems to be limited over time and it is necessary to repeat the treatment after 6 months to maintain good anatomical results and improved BCVA.

From previous studies and our surgical experience in the treatment of CME associated with diabetic retinopathy, retinal vein occlusion, uveitis, and pseudophakic CME, we know that repeat intravitreal triamcinolone injections can lead to several complications such as glaucoma, postinjection infectious endophthalmitis, cataract, rhegmatogenous retinal detachment, and internal limiting membrane thickening.

A new possibility for treating macular edema with corticosteroids has been proposed (phase 3 clinical trials). It consists of a steroid, microsized, biodegradable ocular implant that provides sustained delivery of dexamethasone directly to the target disease site. Ninety days following implantation, patients showed a statistically significant improvement in visual acuity.

A longer follow-up period with repeated injection treatments would be useful to determine if the related benefits of the treatment are sufficient to overcome the risks from the disease. Moreover, when a decrease in CME and central macular thickness occurs, a subthreshold laser macular grid could be useful because anatomical structures are more preserved by a negative laser effect. It also would be useful to repeat the intravitreal injection after 6 months because the visual acuity improvement permits better psychological and functional behavior in patients with this type of disease.

Submitted for Publication: February 27, 2006; final revision received September 28, 2006; accepted October 4, 2006.

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Financial Disclosure: None reported.

REFERENCES


From the Archives of the Archives
Still we hold conflicting views, perhaps because they are many of them founded, not on rigid investigation and experiment, but, as is often unavoidable, on more or less hasty impressions and on prejudice. I may as well say, to begin with, that my prejudice was in favor of boiling instruments. My preference for this was founded, of course, on the overwhelming weight of evidence accumulated by general surgeons from Schimmelbusch down. Still we hold conflicting views, perhaps because they are many of them founded, not on rigid investigation and experiment, but, as is often unavoidable, on more or less hasty impressions and on prejudice. I may as well say, to begin with, that my prejudice was in favor of boiling instruments. My preference for this was founded, of course, on the overwhelming weight of evidence accumulated by general surgeons from Schimmelbusch down.