Photodynamic Therapy with Intravitreal Triamcinolone in Predominantly Classic Choroidal Neovascularization

One-Year Results of a Randomized Study

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Purpose: To determine whether intravitreal triamcinolone acetonide (IVTA) improves the efficacy of photodynamic therapy (PDT) with verteporfin in predominantly classic subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

Design: Prospective randomized study.

Participants: Sixty-one patients with predominantly classic subfoveal CNV secondary to AMD.

Methods: Patients were randomized to receive PDT (n = 30) or PDT followed by approximately 11 mg IVTA (n = 31), with retreatment every 3 months when leakage was documented by fluorescein angiography. At baseline and each follow-up visit, best-corrected visual acuity (VA) was measured with Early Treatment Diabetic Retinopathy Study charts by a certified examiner masked to the patient’s treatment, lesion size on fluorescein angiography, and foveal thickness on optical coherence tomography.

Main Outcome Measures: Mean change in VA (logarithm of the minimum angle of resolution [logMAR]) from baseline, percentage of patients losing fewer than 15 letters (3 lines) of VA, mean change in lesion size, mean change in foveal thickness, and retreatment rate.

Results: At the 12-month follow-up, VA (mean logMAR change from baseline) was significantly better (P < 0.001) in the group of patients who received combined therapy. Seventy-four percent of patients treated with combined therapy compared with 61% treated with verteporfin alone lost fewer than 15 letters of VA (P = 0.78). Reduction in lesion size (P = 0.001) and in foveal thickness (P = 0.03) was significantly greater with combined therapy than with verteporfin. Retreatment rate was significantly lower (P = 0.04) in the combined therapy group. Triamcinolone-related adverse events included glaucoma (25.8%) and cataract progression (32%).

Conclusions: Combined PDT and IVTA therapy seemed to be more effective than PDT alone for managing predominantly classic subfoveal lesions secondary to AMD. The triamcinolone-related adverse events included glaucoma and cataract progression. Ophthalmology 2006;113:2243–2250 © 2006 by the American Academy of Ophthalmology.

Photodynamic therapy (PDT) with verteporfin has shown efficacy in the treatment of predominantly classic subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).1 Nevertheless, leakage resulting from CNV regrowth occurs often, and multiple courses of PDT may be required to limit further visual loss.2 In addition, it is hypothesized that choroidal hypoperfusion after PDT may stimulate the production of local angiogenic factors, such as vascular endothelial growth factor.3 Intravitreal triamcinolone acetonide (IVTA) is a corticosteroid with antiinflammatory and antiangiogenic properties.4 As monotherapy, IVTA has shown a very limited beneficial effect for managing neovascular AMD.5 However, IVTA in combination with PDT yielded favorable results in terms of improved visual acuity (VA) and a lower retreatment rate in a recent pilot study.6,7 We now report the results of a randomized study analyzing the efficacy and safety of IVTA combined with PDT as compared with PDT alone for the treatment of predominantly classic subfoveal CNV secondary to AMD.
Patients and Methods

We conducted this prospective, randomized study at Bellvitge University Hospital, a referral center for AMD patients in Spain. Because intravitreal use of triamcinolone acetonide is not approved in Spain, we obtained a compassionate use indication from the Ministerio de Sanidad y Consumo (Ministry of Health and Consumer Affairs) before initiating the study. All participating patients signed an informed consent form. Each patient underwent distance VA measurement using an Early Treatment Diabetic Retinopathy Study chart by a certified examiner who was masked to the treatment received. An ophthalmic examination was performed, including slit-lamp biomicroscopy, intraocular pressure (IOP) measurement, color fundus photography, red-free fundus photography, digital fluorescein angiography (FA; Imagenet; Topcon Corporation, Tokyo, Japan), and optical coherence tomography (OCT) scanning (Stratus OCT 3; Zeiss Jena GmbH, Jena, Germany). The same experienced ophthalmologist (MB) performed all FA and OCT evaluations. The data recorded included greatest linear dimension (GLD) and area of the lesion on FA, and retinal thickness at the fovea on OCT. Examiners reading the fluorescein angiograms and OCT scans were not masked to the patient’s treatment.

The following inclusion criteria were applied: (1) age 50 years or older, (2) neovascular AMD, (3) CNV under the geometric center of the fovea (subfoveal), (4) area of classic CNV occupied at least 50% of the overall lesion area (predominantly classic), (5) GLD of the lesion less than 5400 μm, (6) baseline visual acuity was the Snellen equivalent of 20/40 to 20/400, and (7) IOP of 21 mmHg or less (if treated, with no more than 1 topical drug). Patients who had received treatment for CNV before the time of enrollment in the study were excluded.

Using simple randomization, participating patients were randomized (1:1) to receive PDT alone or combined with IVTA. All patients received PDT with verteporfin (Visudyne; Novartis Pharma AG, Basel, Switzerland) following the standard treatment protocol. Verteporfin (6 mg/m² body surface area) was administered via intravenous infusion of 30 ml over 10 minutes. Fifteen minutes after starting the infusion, a diode laser light at 689 nm (Zeiss Jena GmbH, Jena, Germany) delivered 50 J/cm² at an intensity of 600 mW/cm² over 83 seconds, using a spot size with a diameter 1000 μm larger than the GLD of the lesion. Patients were instructed to avoid direct sunlight and bright indoor light for 48 hours after treatment.

Triamcinolone acetonide (Trigon Depot; Bristol-Myers Squibb, Anagni Frosinone, Italy) was prepared by our hospital pharmacy department for the intravitreal injection. A filtration and backflush procedure with 5.0-μm porous membrane filters was used to remove most of the additives, mainly benzyl alcohol and carboxymethylcellulose, as described by other authors. A volume of 0.62 ml triamcinolone was drawn from the commercial ampoule and was placed in a tuberculin syringe (1 ml) filled with saline solution. A Millipore (Billericia, MA) filter (pore size, 5.0 μm) was placed on top of the syringe and most of the contents were pressed through the filter, with the triamcinolone crystals remaining in the syringe. The syringe was refilled with saline solution and the same sequence was repeated 3 times. This procedure was carried out 1 hour before the intravitreal injection. The concentration of triamcinolone acetonide in the solution was determined by high-performance liquid chromatography. Analysis of 25 probes prepared by the same technician under the same conditions gave a final mean triamcinolone dose of 10.79 mg/0.1 ml (standard deviation [SD], 4.32 mg/0.1 ml; median, 11.13 mg/0.1 ml).

Patients randomly assigned to IVTA received the injection immediately after the PDT course as an outpatient procedure under sterile conditions using Betadine (Purdue Pharma, Stamford, CT), a drape, gloves, and a lid speculum. The 0.1-ml injection was performed with a 30-gauge needle on a 1-ml syringe. Patients were instructed to instill 4 drops of ofloxacin into the eye every day for 5 days. They were asked to return 3 or 4 days after the injection for

Figure 1. Flowchart of the patients in the study. CNV = choroidal neovascularization; IVTA = intravitreal triamcinolone acetonide; PDT = photodynamic therapy; pred = predominantly.
Corticocapsular cataract: grade 0, clear lens; grade 1, early yellowing of lens, with or without altering VA; grade 2, moderate yellowing of lens with less than 50% of cortex involvement; grade 3, brunescent cataract, with or without extensive cortical changes.

Posterior subcapsular cataract: grade 0, clear lens; grade 1, opacity area involving less than 25% of posterior capsule; grade 2, opacity area involving 25% to 50% of posterior capsule; grade 3, opacity area involving more than 50% of posterior capsule with both direct illumination and retroillumination.

In both groups of patients, the need for retreatment was determined at 3-month intervals based on FA evidence of leakage. When leakage was detected, patients were retreated with the same therapy they received at baseline.

The main end points of the study included the mean change in VA from baseline expressed as the logarithm of the minimum angle of resolution (logMAR; primary endpoint), percentage of patients losing fewer than 15 letters (3 lines) of VA, mean change in foveal thickness (FT), and retreatment rate. Secondary end points were the percentage of patients gaining ≥5, 10, and 15 letters of VA; percentage of patients losing ≥30 letters of VA; and triamcinolone-related adverse events.

Randomization and statistical analyses were performed by independent staff members of our hospital’s Preventive Medicine Department. Baseline comparisons were carried out with analysis of variance for continuous variables and the chi-square test for binary variables. Changes relative to baseline in visual acuity and lesion parameters were evaluated with analysis of variance, the chi-square test, or the t test, as appropriate. Significance was set at a P value of less than 0.05.

Results

Sixty-one patients were assigned randomly to PDT combined with IVTA (n = 31) or PDT alone (n = 30; Fig 1) between March,
2004, and December, 2004. The 12-month follow-up was completed in 31 patients (100%) in the combined therapy group and in 26 patients (86.6%) in the PDT group. There were no statistically significant differences in baseline values between the 2 treatment groups with respect to age, gender, eye, lens status, hypertension, smoking, VA (logMAR), IOP, glaucoma, GLD, lesion area, or FT (Table 1).

At baseline, mean VA (logMAR) was 0.95 (SD, 0.24) in the combined therapy group (approximately 20/160 Snellen equivalent) and 1.07 (SD, 0.25) in the PDT group (approximately 20/200 Snellen equivalent). At the 12-month follow-up, mean VA (logMAR) was 1.04 (SD, 0.24) in the combined therapy group (approximately 20/200 Snellen equivalent) and 1.58 (SD, 0.84) in the PDT group (approximately 20/640 Snellen equivalent; Table 2). Mean VA (logMAR) did not change significantly in the combined therapy group (P = 0.15), but it worsened significantly in the PDT group (P = 0.001). The difference in VA change between the 2 groups was significant (P = 0.001; Fig 2).

The main VA changes are shown in Table 3. At the 12-month follow-up, 74% of patients treated with combined therapy compared with 61% treated only with verteporfin lost fewer than 15 letters (3 lines) of VA (P = 0.78). Two patients (7%) in the PDT group and none of the patients in the combined therapy group lost ≥30 letters (6 lines) of VA (P = 0.58). When the percentages of eyes that improved by ≥5, 10, or 15 letters of VA from baseline were compared, the combined therapy was numerically superior to verteporfin alone, although the statistical superiority seen at month 6 was not observed at month 12.

At baseline, mean lesion size (area) was 5.58 mm² (SD, 3.59 mm²) in the combined therapy group and 6.56 mm² (SD, 5.14 mm²) in the PDT group. At the 12-month follow-up, mean lesion size was 4.16 mm² (SD, 3.88 mm²) in the combined therapy group and 8.65 mm² (SD, 5.36 mm²) in the PDT group (Table 2). At the 12-month follow-up, significant differences between the 2 groups were seen in the lesion size (area, P = 0.001) and GLD change (P = 0.001; Table 2).

A significant reduction in FT was observed in both groups of patients at 12 months. Mean FT decreased from 530 μm (SD, 104 μm) to 356 μm (SD, 121 μm) in the combined therapy group (P = 0.001) and from 552 μm (SD, 149 μm) to 445 μm (SD, 180 μm) in the PDT group (P = 0.04). The reduction in FT between the 2 groups was significantly greater in the patients receiving combined therapy (P = 0.03; Table 2).

The retreatment rate was 1.8 with combined therapy and 2.9 with PDT (P = 0.04). Over the follow-up, fewer patients in the combined therapy group experienced FA-documented leakage (Fig 3). At the 12-month examination in the PDT group, 3 patients (11.5%) had received 1 treatment, 5 patients (19.2%) had received 2 treatments, 9 patients (34.6%) had received 3 treatments, and 9 patients (34.6%) had received 4 treatments. In the combination therapy group, 13 patients (41.9%) had received 1 treatment, 14 patients (45.1%) had received 2 treatments, 1 patient (3.2%) had received 3 treatments, and 3 patients (9.6%) had received 4 treatments. In 28 patients (90.3%) in the combined therapy group, no treatment was necessary during at least 6 consecutive months of follow-up. This supports the idea that the effect of IVTA can last up to 6 months in some eyes.

We observed that some patients with very similar lesions at baseline had a quite different response, depending on which therapy group they were in: those receiving IVTA required fewer treatments to reduce or eliminate leakage and had better visual outcomes (Figs 4, 5). No relevant side effects related to verteporfin therapy were recorded. At the 12-month follow-up in patients receiving an intravitreal injection, there were no cases of endophthalmitis, retinal detachment, vitreous hemorrhage, or traumatic cataract. In patients receiving triamcinolone, an IOP of 24 mmHg or more was documented in 8 patients (25.8%) during the follow-up. Three of these patients (37.5%) had glaucoma at baseline. In 4 patients (50%), glaucoma appeared after a reinjection. These patients were given topical medication (1 or 2 drugs) to control IOP. Glaucoma surgery was not necessary in any patient.

At 12 months, some degree of cataract progression was documented in 8 of 25 phakic patients (32%) in the triamcinolone group. Two of the patients were scheduled for cataract surgery.

### Discussion

This prospective, randomized study examining the efficacy of IVTA combined with PDT found a potential benefit of this approach at 12 months in the management of predominantly classic subfoveal CNV secondary to AMD. Mean VA

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**Table 3. Changes in Visual Acuity**

<table>
<thead>
<tr>
<th>Change in Visual Acuity</th>
<th>Month 3, No. (%)</th>
<th>Month 6, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Photodynamic Therapy</td>
<td>Photodynamic Therapy plus Intravitreal Triamcinolone</td>
</tr>
<tr>
<td>Loss &lt;15 letters</td>
<td>25 (89.2)</td>
<td>27 (87)</td>
</tr>
<tr>
<td>Loss ≥15 letters</td>
<td>3 (10.7)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Loss ≥30 letters</td>
<td>1 (3.5)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Gain ≥0 letters</td>
<td>12 (42.8)</td>
<td>20 (64.3)</td>
</tr>
<tr>
<td>Gain ≥5 letters</td>
<td>4 (14.2)</td>
<td>13 (41.9)</td>
</tr>
<tr>
<td>Gain ≥10 letters</td>
<td>2 (7.1)</td>
<td>8 (25.8)</td>
</tr>
<tr>
<td>Gain ≥15 letters</td>
<td>1 (3.5)</td>
<td>4 (12.9)</td>
</tr>
</tbody>
</table>

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**Figure 3.** Bar graph showing percentage of cases with leakage documented on fluorescein angiography during the study. IVTA = intravitreal triamcinolone acetonide; PDT = photodynamic therapy.
(logMAR) change from baseline was significantly better in patients receiving combined therapy as compared with patients treated with PDT alone. No significant difference was found between the groups regarding loss of fewer than 15 letters of VA. However, the estimated sample size required to show statistical significance in this end point was 200 patients randomized 1:1 to either PDT or PDT combined with IVTA.

Combined therapy resulted in a significantly greater reduction in lesion size than verteporfin alone. In addition, a significantly greater decrease in FT was documented in the combined therapy group. Optical coherence tomography scans are highly useful for determining any degree of macular edema, and it is known that IVTA is a powerful drug for reducing edema. Therefore, CNV associated with relatively low interocular variation in the reduction of triamcinolone dosage is possible depending on the method used, whereas the intrapharmacy variation in the reduction of triamcinolone dosage is relatively low. This may account for the variability among the published studies. Based on the favorable experience of other authors, we decided to use a filtering technique. It is uncertain whether and how much the filtering process reduces the amount of triamcinolone ready for intravitreal injection. It has been reported that preparation of triamcinolone acetone shows marked interpharmacy variation depending on the method used, whereas the intrapharmacy variation in the reduction of triamcinolone dosage is relatively low. This may account for the variability among the published studies. Thus, standardized preparation of triamcinolone probes by the same pharmacy is warranted. High-performance liquid chromatography analysis in our study showed that approximately 11 mg triamcinolone acetone was injected. We considered it interesting to test this dose, because it is intermediate between the 2 most highly investigated doses (4 mg and 20–25 mg).

The duration of the therapeutic effect of IVTA has not been defined completely, but it seems to be important to keep the intravitreal concentration of steroids relatively high to prevent further CNV growth. That is why we decided to reinject every 3 months if necessary, depending on evidence of leakage on FA analysis. Nevertheless, we do not know how many IVTA injections the eye will tolerate at this dose.

The degree of cataract progression was mild in our study and did not lead to substantial changes in VA except in 2 patients, who were scheduled for surgery. Nevertheless, the potential clinical significance of the cataract progression should be taken into account, because it may have adversely affected the final visual outcome in the combination treatment arm. It has been reported recently that single IVTA injections may induce posterior subcapsular cataract development, whereas multiple injections result in all-layer cataract progression.

As other authors have done, we defined glaucoma as an IOP of 24 mmHg or more. In the present study, 37.5% of patients with this adverse event at presentation had baseline glaucoma, which was being controlled (IOP ≤21 mmHg) with a single topical drug. It has been described that the proportion of patients in whom a pressure elevation develops to at least 24 mmHg after IVTA injection is much higher for those with a baseline IOP of 15 mmHg or more. However in 50% of
Figure 4. Images of a 79-year-old man with a 4-week history of decreased vision in his left eye. Visual acuity was 20/200. A, Fundus examination image revealing loss of the foveal reflex with evidence of subretinal fluid. B, Early angiographic image showing a well-delineated fluorescent area with (C) late leakage consistent with predominantly classic choroidal neovascularization (CNV). D, Horizontal scan through the foveal center showing extensive intraretinal cystic edema and an external, highly reflective band appearing thinned and discontinuous with apparent splitting centrally, possibly identifying the CNV. The patient was randomized and allocated to photodynamic therapy combined with intravitreal triamcinolone acetonide. At the 12-month follow-up, the patient had received 2 combined treatments. Visual acuity was 20/63. E, Fundus examination revealing flattening of the foveal center with no evidence of subretinal fluid. F, G, Fluorescein angiographic images showing decrease in the size of the lesion and late staining. H, Repeat scan through the foveal center revealing a flattened foveal contour with an intraretinal cystic cavity and the highly reflective external band corresponding with the area of classic CNV appearing thickened and more sharply demarcated.
Figure 5. Images of a 64-year-old man with a 6-week history of decreased vision in his right eye. Visual acuity was 20/250. Results of (A) fundus examination, (B, C) fluorescein angiography examination, and (D) optical coherence tomography were very similar to those described in Figure 4. The patient was randomized and allocated to photodynamic therapy. At the 12-month follow-up, the patient had received 4 combined treatments. Visual acuity was 20/320. E, Repeat fundus examination revealing atrophic changes of the foveal center with some fluid. F, G, Fluorescein angiography images showing increase in the size of the lesion and late leakage. H, Repeat scan through the foveal center revealing a thin retina with mild cystoid intraretinal edema and a highly reflective external band corresponding to the area of classic choroidal neovascularization that appears to be thickened.
patients, glaucoma developed after administration of a reinjection.23 None of our patients experienced endophthalmitis. To minimize this complication, it is very important to perform the injection under sterile conditions.24,25 Likewise, there were no cases of pseudoendophthalmitis; this may be related to elimination of vehicle in the triamcinolone suspension before intravitreal use.

The current study has some limitations that must be recognized. We enrolled patients in a single center and we tested a single dose of triamcinolone. Perhaps a lower dose might have shown the same efficacy with fewer adverse events. Another limitation is that angiograms and OCT scans were not evaluated by masked graders. Moreover, patients allocated to PDT did not receive a sham injection. The only masked participant in this study was the certified vision tester. Several well-designed clinical trials evaluating this combined therapy are under way. We should await the results of these trials to determine with greater confidence the relative degree of efficacy and safety offered by the 2 treatment regimens.26

To conclude, a potential benefit in VA at 12 months was found with the use of IVTA combined with PDT in the management of predominantly classic subfoveal CNV secondary to AMD. However, in view of the side effects of steroids, the lack of data at 2 years or longer, and the lack of differences in one of the main end points of our study (percentage of patients losing fewer than 15 letters of VA), caution is warranted before recommending this combination therapy.

References