Intravitreal bevacizumab combined with single-session photodynamic therapy and intravitreal triamcinolone acetonide for exudative age-related macular degeneration

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Abstract:

Background: To evaluate the efficacy of intravitreal bevacizumab (IVB) combined with single-session photodynamic therapy (PDT) and intravitreal triamcinolone acetonide (IVT) as the initial treatment and the use of repeat IVB for visual gain maintaining in neovascular age-related macular degeneration (AMD).

Methods: In a prospective interventional case series, patients with subfoveal choroidal neovascularization (CNV) secondary to AMD underwent pulse therapy with single-session PDT according to the standard protocol followed by 1.25mg IVB and 2mg IVT 48 hours later. Best corrected visual acuity (BCVA) assessment, optical coherence tomography (OCT) and fluorescein angiography (FA) were performed prior to treatment. Visual acuity and OCT measurements were repeated at 6 week intervals and FA was performed at 12 weeks and as considered necessary thereafter. Repeat injection of IVB was performed based on fluorescein angiographic evidence of CNV leakage.

Results: Seventeen eyes of 17 patients with the mean age of 68 years underwent combination therapy. Mean follow up was 20.4 weeks. The mean BCVA prior to treatment was 0.74±0.33 logMAR and mean central macular thickness (CMT) was 394.72±180.55µ. At week 12, the mean BCVA was 0.54 ± 0.34 logMAR which showed statistically significant difference compared to pretreatment BCVA (P=0.013). Central macular thickness reduced significantly 6 and 12 weeks after the initial treatment (p=0.005 and p=0.028 respectively). Visual acuity improvement and CMT reduction persisted during the follow-up. The second intravitreal injection of bevacizumab was required in 8 eyes with mean interval of 14.25 ± 3.57 weeks. Rise in intraocular pressure was noticed in one patient which was controlled with topical medications.

Conclusion: Pulse therapy consisting of IVB combined with single-session PDT and single-injection IVT improves vision and may decrease the need for
retratements in neovascular AMD. Repeat IVB injection maintains visual gain that results from the initial combination therapy.

**Key words:** age related macular degeneration, bevacizumab, combination therapy, photodynamic therapy.
**Introduction:**

Photodynamic therapy (PDT) with verteporfin is a standard treatment for neovascular age-related macular degeneration (AMD) [1-3]. Selective photothrombosis of the CNV has been mentioned as a potential benefit of PDT. However, it is not completely selective for neovascular endothelia and may also affect the normal choroidal vasculature [4,5,6,7]. Definite choriocapillary closure has been reported in human eye after PDT using the standard treatment parameters. This hazardous effect reaches its maximum 1 week after treatment. After 3 months, partial reperfusion of the choriocapillaris layer is apparent [5]. Repeated photodynamic therapy however, results in a persistent choriocapillary non-perfusion in most cases [4].

Photodynamic therapy with verteporfin stabilizes the patient’s vision rather than improve it [1-3]. In addition to that, the need for numerous retreatments with its hazardous effects on choriocapillary perfusion and concerns about the cost are important drawbacks of monotherapy with PDT. Recent studies have shown that combining intravitreal triamcinolone with PDT has superiorities to monotherapy in terms of positive changes in visual acuity (VA) and less need for retreatments [8-13]. It has also been suggested that antiangiogenic drugs may be combined with PDT as an efficacious treatment modality [10]. We performed a pilot study to evaluate the results of pulse therapy with intravitreal bevacizumab combined with single-session verteporfin therapy and single- injection intravitreal triamcinolone in all types of neovascular AMD. Repeat injection of IVB was used for the maintenance of visual gain. Herein, we report the short results of this therapeutic approach.
**Methods:**

The study was a prospective, interventional case series. The treatment protocol was approved by the local ethics committee. Patients were informed about the risks and benefits of combined therapy and written consent was obtained. Eyes with all types of active subfoveal CNV secondary to neovascular AMD with lesions less than 4 MPS disc area and Snellen VA equivalent of 20/40 to 20/400 at baseline were included. Patients were excluded if they had history of glaucoma, diabetic retinopathy or any other type of macular disease.

Eligible eyes were evaluated before treatment completely. Best corrected visual acuity (BCVA) was assessed using Snellen chart. Applanation tonometry, anterior segment examination with slit lamp and fundus examination was performed. All eyes underwent color fundus photography and fluorescein angiography (FA) using a confocal scanning laser angiograph (Heidelberg retina angiograph II: Heidelberg engineering). Optical coherence tomography (Zeiss, Dublin, CA), was performed before intervention for all cases to measure the central macular thickness (CMT). Photodynamic therapy with verteporfin was performed according to the standard regimen. Forty eight hours after PDT, intravitreal injection of 1.25mg/0.05ml bevacizumab (Avastin, made for F. Hoffmann-La Roche Ltd Basel, Switzerland by Genentech, Inc., San Francisco, CA) and 2mg/0.05ml triamcinolone acetonide was carried out at two different sites under sterile condition. A topical antibiotic, every 6 hours for 3 days, was prescribed and patients were instructed to return in case of ocular pain or redness or any deterioration of vision. Patients were examined one day and one week after injection. Topical antiglaucoma medication was prescribed if intraocular pressure (IOP) was more than 21 mmHg.

Evaluation of visual acuity and optical coherence tomography (OCT) was repeated in 6 week intervals. Fluorescein angiography was repeated at week 12 and when considered necessary thereafter. Decision about retreatment was made based on CNV activity. Eyes with active CNV leakage on FA underwent repeat
intravitreal injection of 1.25mg bevacizumab. Neither repeat PDT nor repeat intravitreal injection of triamcinolone was considered in the protocol.

Paired T-test was used to compare findings between before and after treatment.
Results

Seventeen eyes of 17 patients (7 male and 10 female) with the mean age of 68 years (range 51-82) were included in this study. Lesion types were dominantly classic in 5 eyes, minimally classic in 3 eyes, occult in 8 eyes and retinal angiomatous proliferation in one eye. Mean follow-up was 20.4 weeks (minimum: 12 weeks).

Mean BCVA was 0.74 ±0.33 logMAR (range: 1.20 to 0.20) before treatment. BCVA improved to 0.54±0.34 at week 12 following treatment (P=0.013). Further improvement to 0.34± 0.30 logMAR and 0.30±0.31 logMAR was observed at weeks 18 and 24 respectively (Figure 1). BCVA improved in 10 eyes (58.8%) and remained unchanged in 7 eyes (41.2%) 12 weeks after the initial therapy. Mean central macular thickness (CMT) was 394.72±180.55µ prior to treatment. Mean CMT reduced to 212.6±58.6µ after 6 weeks and 225.18±79.21µ at week 12 (p=0.005 and p=0.028 respectively). CMT reduction persisted during the follow-up period (Figure 2).

Nine eyes (52.9%) remained stable following the initial therapy. A second intravitreal injection of bevacizumab was required in 8 eyes (47.1%) and a third injection was performed in 3 eyes. The mean interval between the first and second injections were 14.25± 3.57 weeks. This interval had a range of 12 to 18 weeks in eyes that underwent the third injection. No ocular or systemic adverse events were observed.

Mean IOP was 14±1.92 mmHg before treatment. Mean IOP rose to 17.33±6.28 mmHg at weeks 6 and returned to pretreatment level 12 weeks after intervention. In one patient IOP rose to 34 mmHg after one week. The intraocular pressure was controlled in this patient with a combination of timolol eye drop bid and dorzolamide eye drop every 8 hours, which were continued for 5 weeks.
Discussion:

In this small case series, combination of intravitreal bevacizumab with PDT and intravitreal triamcinolone acetonide was used as pulse therapy for neovascular AMD. Our purpose was to increase the efficacy of treatment and reduce the side effects of monotherapy. Combination therapy resulted in significant visual improvement and CMT reduction irrespective of lesion type. This treatment modality also reduced the need for retreatments.

Photodynamic therapy with verteporfin induces a photothrombosis of the choroidal neovascularization. The possible adverse effects of PDT on physiological choroid were underestimated in the PDT trials because FA was the only angiographic modality [1-3]. Dose-related damage to the choriocapillaris was detected later by analysis of ICG images [4,6]. Subsequent studies revealed the occurrence of choriocapillary layer occlusion manifesting as an area of hypofluorescence during both early and late-phase ICG angiograms [5,6]. The size of hypofluorescence was largest 1 week after PDT and decreased gradually during follow up. Recovery happened in most cases after 12 weeks. However, a residual change in the choroidal filling pattern often persisted during long-term follow up. There was a tight correlation between persistent and intense hypofluorescence and retinal sensitivity with a larger and more intense scotoma being associated with more intense hypofluorescence [14].

One of the drawbacks of PDT is the need to multiple retreatments [1-3]. In a study by Schmidt- Erfurth et al, the effects of multiple- PDT regimen was evaluated [5]. Persistent hypofluorescence was documented in all patients after the second and third PDT. Quantitative analysis showed a 25% enlargement of the hypofluorescent area one week after the second PDT compared with the area measured after the first PDT [5]. In addition to the choriocapillary layer, repeat PDT may also have an accumulating adverse effect on RPE and sensory retina [15,16].
There has been an insight into the issue of persistence and recurrence following PDT, with the help of ICG angiography. In a prospective study, Schmidt-Erfurth et al noticed that choroidal neovascularization remain patent in approximately one half of the PDT-treated eyes manifesting as persistence. Patent feeder vessels are the origin of recurrence in the other 50% of lesions [5]. Repeat PDT may reduce the size of CNV; however, recurrence occurs with the same rate and speed as after a single treatment. In addition to that, the outcome of PDT seems to be worse in the retreatment group compared to single treatment group [5]. Multiple sessions of PDT may accelerate the risk of CNV recurrence due to aggravation of choroidal ischemia and subsequent over-expression of VEGF. We limited PDT to one session in our treatment strategy for two purposes: 1- To reduce the potential side effects of PDT on the physiologic choroidal vasculature, RPE and neurosensory retina; 2- To provide a cost-effective therapeutic modality.

PDT may contribute to the phototoxicity induced VEGF expression and increased permeability by triggering the generation of free radicals and lipid peroxides. Increased VEGF and VEGFR release following PDT may be related to choroidal hypoperfusion [17]. Combination therapy may be a promising option with the purpose of reducing PDT-induced VEGF release. The presence and interaction of stimulatory and inhibitory agents have important clinical implications for treatment strategies. Combination of IVB and IVT with photodynamic therapy may counteract the stimulatory effects of PDT induced release of VEGF and VEGFR and enhance the inhibitory effect of PEDF. The interaction of bevacizumab and triamcinolone acetonide with PEDF necessitates further investigations.

Triamcinolone is an angiostatic steroid which has an inhibitory effect on choroidal microvascular endothelial cells migration and tube formation [18]. Triamcinolone has been shown to suppress early proangiogenic response in RPE cells after PDT in vitro. VEGF was increased and PEDF reduced in cultured RPE
cells shortly after PDT. Triamcinolone acetonide suppressed this proangiogenic response [19].

In addition to combating some of the PDT-induced adverse effects IVT may independently affect CNV. Intravitreal triamcinolone monotherapy has been used for treatment of neovascular AMD [20-22]. There has been modest beneficial effect in the short term. The long-term results of these studies however have revealed no beneficial effect. A number of pilot studies have evaluated the results of combination therapy with PDT and intravitreal triamcinolone [8-13]. These studies have reported the effects of 4mg or 25mg triamcinolone injection after PDT and have shown promising results. The potential complications of IVT however induce safety concerns. Two most significant side effects of IVT are glaucoma and cataract. Significant IOP elevation (ie, IOP>21 mmHg or requiring medical or surgical therapy) has been reported in 21% to 43% of eyes undergoing either 4 mg or 25mg IVT injection [20-22]. Repeat injections of IVT are associated with more severe IOP rise [22,23]. There was no statistically significant difference between mean IOP before and after IVT injections in our series. Significant IOP elevation was observed only in one patient which was controlled with topical medications. The optimal dose of IVT is not obvious at present. The standard dose of 4mg may induce a vitreous concentration approximately 20000 times that needed to completely saturate all triamcinolone receptors in the cell cytoplasm [24,25]. The concentration of triamcinolone in the subretinal space however, is not known. We limited the intravitreal triamcinolone to one injection and used a lower dose to reduce the adverse effects. By 2mg dose of IVT, the total volume of intravitreal injections reduced to 0.1cc (0.05cc IVT and 0.05cc IVB). We could not evaluate the cataract inducing effect of 2mg IVT because of short follow-up of our patients.

Intravitreal injection of bevacizumab may result in visual improvement, decreased retinal thickness and reduction in angiographic leakage [26]. Monotherapy with bevacizumab however necessitates multiple intravitreal
injections within 4-6 week intervals. Every intravitreal injection constitutes the potential risks of serious complications. Use of an antiangiogenic factor can counteract the PDT induced over-expression of VEGF and reduce its adverse effects. On the other hand, PDT causes breakdown of the CNV vascular barrier and may help the antiangiogenic factor to affect the lesion more potently.

**Conclusion:**

Our preliminary results suggest that intravitreal bevacizumab has a synergistic effect with PDT and intravitreal triamcinolone. Using this combination therapy as a pulse can result in partial or complete regression of CNV and improvement or stabilization of visual acuity. In case of CNV persistence or recurrence, repeat intravitreal injection of bevacizumab may help maintaining the visual gain. Results of our study using this type of treatment strategy are encouraging. This study however has numerous shortcomings. The study weaknesses refer to the small number of patients, absence of control groups and short follow-up period. Further studies are required to confirm the results of this small pilot study.
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Figure legends:

**Figure 1:** Significant visual improvement occurred after 12 weeks and continued during the follow-up period.

**Figure 2:** Significant reduction of CMT was observed at week 6 and persisted during the follow-up
CMT in OCT (microns)

before  | week6   | week12  | week18  | week24  
---------|---------|---------|---------|---------
         |         |         |         |         

Figure 2