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Efficacy and Safety of Combined Intravitreal Bevacizumab and Retrobulbar Corticosteroids for Neovascular Age-Related Macular Degeneration

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Abstract

Introduction: Inflammation plays an important role in age-related macular degeneration (AMD) pathogenesis and progression. Thus, corticosteroids have been used for macular edema associated with exudative AMD. The purpose of this study was to evaluate the efficacy and safety of combined therapy of Intravitreal Bevacizumab (IVB) with Retrobulbar (RB) injection of triamcinolone or dexamethasone (RBTA or RBDEX) in eyes with Choroidal Neovascularization (CNV) in AMD. Secondary, we compared the results with the efficacy of single intravitreal injection of bevacizumab, ranibizumab and aflibercept.

Methods: In this retrospective interventional comparative case series, patients with CNV were treated with IVB (1.25 mg) and RBTA or RBDEX. Control groups included patients who underwent IV injection of Bevacizumab (IVB), Ranibizumab (IVR) and Aflibercept (IVA). The primary purpose was the change of Central Retinal Thickness (CRT) at the Optical Coherence Tomography (OCT) and of Best Corrected Visual Acuity (BCVA) at 1 year.

Results: A total of 123 eyes were divided into Group 1 (31 eyes treated with IVB+RBTA); Group 2 (31 IVB +RBDEX); Group 3 (25 IVB), Group 4 (24 IVA); Group 5, (12 IVR). All 5 groups showed a statistically significant improvement at 1 year in terms of visual acuity and CRT reduction. Group 1 showed significant greater gain of letter at 1-year (13.06 letters) compared to group 3 (8.24 letters, p=0.04) and to group 5 (6.58 letters, p=0.045). Combined therapy showed statistically significantly greater CRT reduction compared to the IVB (mean CRT reduction at 1-year: 71.39 µm, 75.84 µm and 38.44 µm in group 1, 2 and 3) with a lower number of injections per year.

Conclusions: In AMD patients, combined therapy (IVB+RBTA or RBDEX) improved visual acuity with a minimum number of treatments during the 1-year follow-up. Prospective studies with a larger sample are needed to confirm these results and determine the long-term efficacy of this therapy.

Keywords: Anti-VEGF; Neovascular AMD; Combined therapy

Introduction

Age-related Macular Degeneration (AMD) is one of the major irreversible cause of visual loss in the elderly population, affecting almost 30-50 million people worldwide [1,2]. Moreover, the prevalence of AMD is rising due to the increasing of lifespan [2]. Choroidal Neovascularization (CNV) is the hallmark of exudative AMD (wet subtype) and causes macular bleeding and exudation. Although exudative AMD accounts for 10-20% of all AMD patients, it is the most debilitating and rapidly progressive form with severe vision loss in most patients [3,4].

AMD is a complex and multifactorial disease in which many factors have been identified, such as genetic inheritance, ageing, environment, oxidative stress and inflammation [5]. Inflammatory cells and cytokines play an important role in AMD pathogenesis and progression [6]. In addition to the anti-inflammatory effects, corticosteroids reduce the permeability of choroidal endothelial cells and suppress VEGF expression [7].

Thus, corticosteroids have been used for macular edema associated with exudative AMD both as an alternative and in combination to Anti-Vascular Endothelial Growth Factor (VEGF) therapy [8-17]. Most studies showed their effectiveness in improving vision function and reducing macular edema. Nevertheless, intravitreal injection of corticosteroids carries significant complication risk such as cataract progression, ocular hypertension and endophthalmitis [18-20]. Thus, retro bulbar injections of corticosteroids are a valid alternative to intravitreal injection: it has been demonstrated to provide the same effectiveness in reducing macular edema but with a lower rate of intraocular complications [21-23].

The purpose of this study was to evaluate the efficacy and safety of combined therapy of intravitreal bevacizumab with retrobulbar injection of triamcinolone or dexamethasone in eyes with CNV in AMD. Secondary, we compare the effect of combined therapy with that of single intravitreal injection of bevacizumab, ranibizumab and aflibercept.

Methods

This was a retrospective interventional comparative case series. The study was conducted at the Ophthalmology Clinic of the University of Turin between January 2016 and March 2017. The study adhered to the tenets of the Declaration of Helsinki. Study participants provided written informed consent.

Eligibility criteria included age 50 years or older, study eye with best-corrected ETDRS VA between 20/63 and 20/200 Snellen equivalent and the presence of subretinal fluid, intraretinal fluid, sub-retinal pigment epithelium (RPE) fluid, or a combination of those on optical coherence tomography (OCT).

Exclusion criteria included presence of coexisting pathology causing subfoveal choroidal neovascularization such as myopic CNV or retinal angiomatous proliferation, signs of vitreomacular traction, proliferative diabetic retinopathy. Patients who had any laser procedure within 3 months, ocular surgery within 6 months, corneal or lens opacities that precluded retinal visualization were also excluded.

Patients undergoing combined therapy were treated with an intravitreal injection of 1.25 mg bevacizumab (IVB) associated with injection of triamcinolone acetonide (40 mg, 1 ml, Triacort, Pharmatex Italia Srl, Milan, Italy) or dexamethasone (8 mg, 2 ml, Decadron, Farmaceutici Caber Spa, Pomezia, Italy) in the retrobulbar space in the infero-temporal quadrant using a 27-Gauge needle.

Injections were performed in accordance with standard techniques that included the use of 5% povidone iodine and a sterile lid speculum. Intraocular pressure (IOP) was measured 30 minutes after injection.

Patients treated with single-dose intravitreal anti-VEGF with at least one year follow-up paired by gender, age, and ethnicity was recruited as comparator groups. Intravitreal injection of 1.25 mg of Bevacizumab (Avastin, Genentech, South San Francisco, CA), 0.5 mg of Ranibizumab (Lucentis, Novartis, Basel, Switzerland) and 2 mg of Aflibercept (Eylea, Regeneron Pharmaceuticals, Tarrytown, NY), were included.

One eye per patient was included in the study.

At baseline and follow-up visits, patients underwent complete ophthalmological examination including best corrected visual acuity (BCVA) assessment with 4-meter Early Treatment Diabetic Retinopathy Study (ETDRS) charts, intraocular pressure (IOP), biomicroscopic examination of the anterior and posterior segment and central retinal thickness (CRT) measurements using Spectral-Domain OCT (SD-OCT, RTVue-100, Optovue, Fremont, CA). The CRT was obtained in the central 1 mm of the 5 × 5 mm Macular Map (MM5). Fluorescein angiography (FA) and indocyanine green angiography (ICGA) were performed at the baseline or when a recurrence of CNV was suspected.

At each visit the need for retreatment was evaluated based on BCVA and OCT criteria: presence of macular edema at the OCT, loss of visual acuity, or signs of CNV re-activation were indications for retreatment.

The primary purpose of the study was the change of CRT measured at OCT and of BCVA at 1 year. Secondary aim was the evaluation of adverse effects associated with the procedure, which included systemic and local adverse events (increased IOP, cataract progression, endophthalmitis).

Statistical analysis

The normal distribution of data was verified by Shapiro-Wilk test. Comparisons of baseline and post-injection data were performed with the Wilcoxon Ranks Test for continuous variables. The differences between groups in continuous variables were compared using the Kruskal-Wallis test and the Mann-Whitney test for comparisons between the individual groups. Chi-square test was used for comparing discrete variables between groups as appropriate. Any differences showing a P value of less than 0.05 was considered to be statistically significant.

Results

A total of 123 eyes of 123 patients were included into the study; they were divided into 5 groups:

- 31 eyes received IVB+retrobulbar Triamcinolone acetonide (IVB + RBTA): Group 1
- 31 eyes received IVB+retrobulbar Dexamethasone (IVB + RBDEX): Group 2
- 25 eyes received IVT Bevacizumab (IVB): Group 3
- 24 eyes received IVT Aflibercept (IVA): Group 4
- 12 eyes received IVT Ranibizumab (IVR): Group 5

The baseline characteristics of the 5 groups are summarized in Table 1. No statistically significant differences in term of age, sex and number of previous IVT were found. All patients were Caucasian.

	GROUP 1 (IVB+RBTA)	GROUP 2 (IVB+RBDEX)	GROUP 3 (IVB)	GROUP 4 (IVA)	GROUP 5 (IVR)	P
N (eyes)	31	31	25	24	12	
Age (years)	73.19 ± 9.67	78.00 ± 7.49	76.28 ± 12.42	74.08 ± 12.42	77.33 ± 7.15	0.44*
M/F N (%)	17/14 (55/45 %)	13/18 (42/58 %)	11/14 (44/56%)	8/16 (33/67%)	8/4 (67/33%)	0.31°
Previous IVT (N/patient)	1.87 ± 2.20	1.58 ± 1.69	1.44 ± 1.94	2.33 ± 2.71	2.83 ± 2.40	0.40*
Time from diagnosis (years)	13.65 ± 15.56	13.80 ± 14.52	11.60 ± 7.52	12.00 ± 14.04	13.67 ± 13.45	0.88*
IOP (mmHg)	15.61 ± 2.65	15.90 ± 2.99	14.96 ± 2.51	15.25 ± 2.51	15.08 ± 2.90	0.78*
BCVA baseline (logMAR)	0.68 ± 0.40	0.81 ± 0.42	0.62 ± 0.24	0.72 ± 0.34	0.62 ± 0.36	0.56*
CRT baseline (μm)	348.74 ± 52.12	355.39 ± 92.49	319.00 ± 65.70	332.88 ± 57.30	320.08 ± 54.56	0.24*

All parameters are expressed as mean ± standard deviation. IVT: Intravitreal Injection; IOP: Intraocular Pressure; BCVA: Best-Corrected Visual Acuity; CRT: Central Retinal Thickness
*Kruskal-Wallis test
°Chi-square test

Table 1: Patients demographic and clinical characteristics.

All 5 groups showed a statistically significant improvement at 1 year in terms of visual acuity gain and CRT reduction (mean difference CRT ranged from 20.15 ± 14.70% in group 1 to 11.15 ± 14.88% in group 3) (Table 2).

	BCVA baseline (logMAR)	BCVA 1 year (logMAR)	P*	CRT baseline (µm)	CRT 1 year (µm)	Mean difference CRT (%)	P*
GROUP 1 (IVB + RBTA)	0.68 ± 0.40	0.54 ± 0.33	<0.001	348.74 ± 52.12	277.35 ± 62.49	20.15 ± 14.70%	<0.001
GROUP 2 (IVB + RBDEX)	0.81 ± 0.42	0.61 ± 0.32	<0.001	355.39 ± 92.49	279.55 ± 72.19	19.46 ± 15.55 %	<0.001
GROUP 3 (IVB)	0.62 ± 0.24	0.53 ± 0.22	0.003	319.00 ± 65.70	280.56 ± 67.89	11.15 ± 14.88 %	0.001
GROUP 4 (IVA)	0.72 ± 0.34	0.62 ± 0.32	0.002	332.88 ± 57.30	280.96 ± 44.82	14.15 ± 14.68 %	0.001
GROUP 5 (IVR)	0.62 ± 0.36	0.57 ± 0.35	0.034	320.08 ± 54.56	277.50 ± 38.61	11.36 ± 18.74 %	0.025

All parameters are expressed as mean ± standard deviation. BCVA: Best-Corrected Visual Acuity; CRT: Central Retinal Thickness
*Kruskal-Wallis test

Table 2: BCVA and CRT at baseline and 1-year follow-up.

Figure 1 represented the average VA change (number of letters) after 1 year in the 5 treatment groups. The improvement was greater in the Group 2 receiving IVB+RBDEXA (13.06 ± 9.85 letters). This difference is not statistically significant compared to Group 1 receiving IVB +RBTA (10.81 ± 7.51 letters, p=0.49) and to Group 4 receiving IVA (8.29 ± 5.38 letters, p=0.27), but it is significantly higher compared to Group 3 receiving IVB (8.24 ± 6.43 letters, p=0.04) and group 5 6.58 ± 3.65 letters, p=0.045).

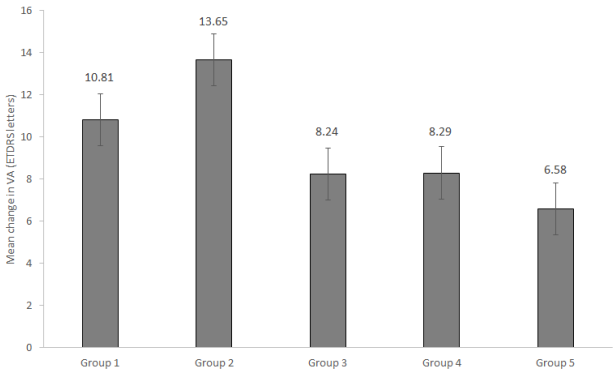

Figure 1: Bar graphs showing the mean visual acuity difference at 12-months visit in comparison to baseline in the 5 different groups.

As shown in Figure 2, 35.4% of eyes in the group 2 showed an improvement ≥ 3 lines at 1 year follow-up, compared to 13%, 16%, 13% and 0% in groups 1, 3, 4 and 5 respectively. None of the patients reported a loss ≥ 3 lines.

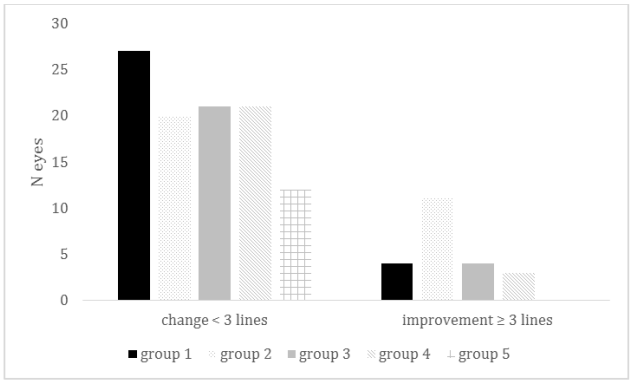

Figure 2: Rate of change in eyes with BCVA improvement of ≥ 3 lines, change and 3 lines at 12 months in each group (p=0.037).

As regard to the structural changes, there were no statistically significant differences found in the mean change of CRT between group 1 and 2 (combined therapy) (Figure 3 and Table 3). Nevertheless, combined therapy with intravitreal bevacizumab and

retrobulbar corticosteroids (both triamcinolone and dexamethasone) showed a greater reduction in CCT compared to single Bevacizumab intravitreal injection (group 3, -38.44 µm, $p_{group\ 1}$ *vs.* 3=0.016, $p_{group\ 2}$ *vs.* 3=0.04).

	Group 1	Group 2	Group 3	Group 4	Group 5
Group 1	-	p= 0.63	p=0.016 *	p=0.14	p= 0.17
Group 2		-	p=0.04 *	p=0.33	p=0.38
Group 3			-	p=0.70	p=0.36
Group 4				-	p=0.83
Group 5					-
Mann-Whitney test, * statistically significant difference					

Table 3: P values between groups comparisons of the mean CRT reduction at one year from baseline.

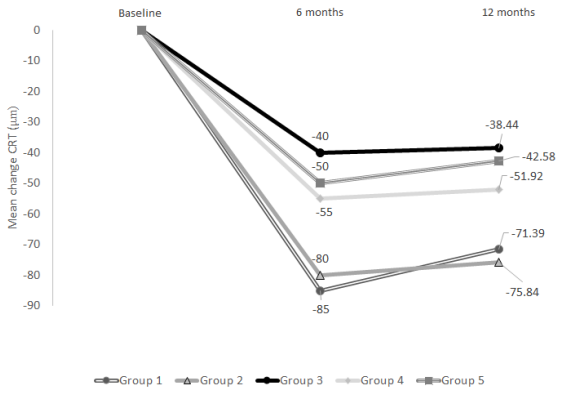

Figure 3: Mean CRT differences at 12 months compared to baseline in the 5 groups.

During the 1-year follow-up the average number of intravitreal injection varies from 3.13 ± 1.91 (group 2) to 4.92 ± 2.00 (group 3), with statistically significant difference between groups (Figure 4).

In terms of safety analysis, no patient had systemic adverse events. No endophthalmitis occurred during the postoperative follow-up period. Transient IOP ≥ 21 mmHg (G) in the 24 h following injection occurred in equal proportions in different groups (22.6% in Group 1, 19.4% in group 2, 16.0% in group 3, 16.7% in Group 4, 16.7% in group 5, p=0.06). All cases were resolved with local therapy. At one year follow-up visit, no patient had elevated IOP. There was no statistical difference in the number of cataract progression (9.7% in Group 1, 6.5% in Group 2, 12.0% in Group 3, 12.5% in Group 4, 8.3% in Group 5, p=0.06). Only one patient in Group 1 had a retrobulbar hemorrage, which reabsorbed in 10 days without sequelae. No other local adverse events (hemovitreous, retinal or choroidal detachment, cranial nerve paralysis) had been recorded.

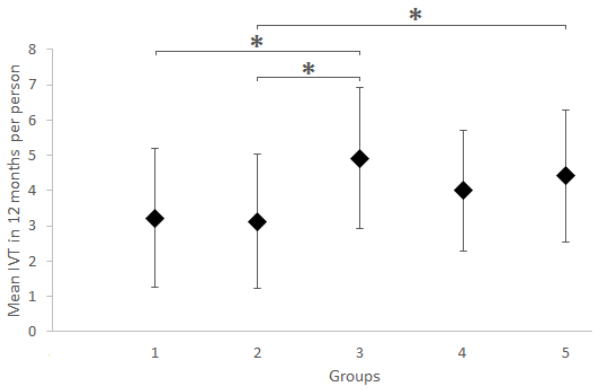

Figure 4: Mean number of treatments per patient during 1 year follow-up. *statistically significant difference between groups.

Discussion

The efficacy of anti-VEGF therapy, already widely demonstrated in *in-vitro* and *in-vivo* studies, showed fewer efficacies in real life studies than in clinical trials [19]. In recent years, many efforts were computed to find new drugs that can overcome the effectiveness of those available in the AMD therapy [20,21].

In the present study, all 5 groups undergoing different protocols showed a significant increase in visual function and a reduction in macular thickness in Caucasian patients with neovascular AMD.

Group 1 receiving IVB+RBTA showed the highest mean percentage decrease in CRT measured with OCT (mean reduction compared to CRT baseline: 20.15% ± 14.70%). This decrease was statistically higher than that of group 3 receiving IVB (mean reduction compared to CRT baseline: 11.15% ± 14.88%, p=0.02). Addition of retrobulbar injection of triamcinolone acetonide to intravitreal bevacizumab statistically reduced the mean number of IVT per patient (3.23 ± 1.96 *vs.* 4.92 ± 2.00 respectively, p=0.002).

Even greater benefits emerged from IVB+RBDEXA therapy in comparison to intravitreal bevacizumab alone. Patients treated with the above mentioned combined therapy showed greater reduction in mean CRT and less IVT per patient per year and a significant visual acuity gain in comparison to Group 3 (BCVA gain in logMAR, -0.20 ± 0.19 and -0.09 ± 0.12 in group 2 and 3 respectively, p=0.04).

The rationale for the use of corticosteroids in CNV therapy lies in the well-proven role of inflammation in the pathogenesis and progression of AMD [6,22].

In a recent *in-vitro* study [23], corticosteroids used in ophthalmological therapy have demonstrated an antioxidant activity on cells similar to Human Epithelium Pigmented Retinal (EPR) cells. Specifically, dexamethasone has been shown to be more protective against EPR cells than acetonide triamcinolone. The results of our study showed an improvement in terms of one-year follow-up visual acuity for the group treated with IVB plus dexamethasone compared to Triamcinolone. Although this difference has to be confirmed, a possible explanation might be the greater ability of Dexamethasone to inhibit the formation of glutathione and to reduce the oxidative stress of the EGP.

In addition to anti-inflammatory and anti-oxidant effects, corticosteroids are able to suppress the expression of VEGF [18], enhancing the effect of anti-VEGF.

In vitro studies [24] have also shown that inflammation in neurodegenerative diseases is related to changes in the blood-brain barrier. Even in the pathogenesis of retinal inflammation in AMD, disruption of metabolites and cytokines from the central nervous system may play a role [25]. For this reason, injection of cortisone in the retrobulbar space would have a further advantage over intravitreal injection due to blockade of retrograde inflammation.

The use of corticosteroids in AMD has already been studied in other studies. Intravitreal dexamethasone, in triple therapy (along with a PDT and anti-VEGF), has been proved to reduce the number of anti-VEGF injections and to stabilize visual acuity [7-9]. In the present study, the combined therapy of retro-bulbar Dexamethasone (with lower risks than intravitreal injection) and intravitreal Bevacizumab has reduced the need of injections maintaining good letter improvement compared to solo intravitreal Bevacizumab. Therefore, although direct comparative studies of the two methods are needed, IVB and RBDEXA combined therapy would seem to be not less effective than triple therapy.

This study presents several limitations including retrospective nature and lack of masking of patients and staff. Another limitation is that many patients already received anti-VEGF and, therefore, their response to therapy may be different from that of naïve patients.

In conclusion, the present study showed significant efficacy in term of visual acuity improvement and CRT reduction in subjects treated with combined therapy (IVB+dexamethasone or triamcinolone RB) compared to the single intravitreal therapy of bevacizumab in eyes with CNV. Although no differences were observed between the two combined therapy groups, group 2, receiving IVB+RBDEXA, showed a greater gain in terms of BCVA than single IVB therapy.

Because this study included a small sample size with a limited follow-up period and it was a retrospective and non-controlled case series, prospective studies with a larger sample are needed to confirm the results of the present study and determine the long-term efficacy of these combined therapies.

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