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Comparison of Combined Bevacizumab plus Dexamethasone *Vs.* Ranibizumab Monotherapy as First-Line Therapy in Patients with Treatment Naive Neovascular Age-Related Macular Degeneration in Real-Life Clinical Practice: A Retrospective Case-Series Analysis

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Abstract

Purpose: To identify the differences between combination bevacizumab plus dexamethasone and ranibizumab in treatment naïve neovascular age-related macular degeneration in terms of functional/morphological outcomes and number of injections when evaluated in real-life clinical practice.

Methods: We compared two groups of patients either receiving intravitreal bevacizumab (1.25 mg) plus dexamethasone sodium phosphate (0.2 mg) or intravitreal ranibizumab (0.5 mg) over a 12 month period. The former, Group A, received treatment at baseline and followed a pro re nata (PRN) regimen. The latter, Group B, received treatment at baseline followed by two additional monthly injections as per the universally accepted protocol whilst continuing treatment on PRN regimen thereafter. Best-corrected visual acuity (BCVA), intraocular pressure (IOP), slit-lamp fundus examination and central macular thickness (CMT) *via* optical coherence tomography (OCT) were recorded at the initial visit (Baseline, BSL) and at each subsequent follow-up visit.

Results: CMT at BSL was 362.8 ± 45.4 μm in Group A and 358.3 ± 47.2 μm in Group B. At the end of the data analysis, CMT was improved substantially in both groups (246.1 ± 42.4 μm in Group A, 254.9 ± 21.2 μm in Group B), while BCVA improved as well (From 0.87 ± 0.15 logMAR to 0.48 ± 0.15 in Group A, from 0.81 ± 0.20 logMAR to 0.52 ± 0.10 in Group B). Group A received 248 injections, whereas Group B received 313.

Conclusion: Combination treatment with DSP and bevacizumab provided the same efficacy and allowed a statistically significant reduction in the frequency of injections compared with ranibizumab monotherapy.

Keywords: Bevacizumab; Dexamethasone; Ranibizumab; Neovascular Age-Related Macular Degeneration; Avastin; Lucentis: Anti-VEGF

Introduction

Age related macular degeneration (AMD) is a major cause of legal blindness in elderly individuals in the western world [1-4]. It affects the macula, initially with characteristic retinal pigment epithelium (RPE) changes (mottling, hyper/hypopigmentation) and drusen deposition (dry AMD). Of note is the presence of a series of inflammatory factors between the RPE and Bruch's membrane [5]. The progression of AMD leads either to late stage geographic atrophy of the macular RPE, or to neovascularization (neovascular AMD), due to vascular endothelial growth factor (VEGF) production [6].

Neovascular AMD is the most vision-threatening form of the disease [7,8]. Visual impairment in neovascular AMD is caused by the formation of a choroidal neovascular membrane (CNV) beneath the macula with consequent subretinal leakage, hemorrhage and intraretinal fluid accumulation. Inflammatory factors and VEGF are the main contributing mediators involved in the progression of AMD, participating in a vicious cycle involving hypoxia, oxidative stress, inflammation, edema and neoangiogenesis.

The cardinal mediator of neovascular AMD is VEGF which is responsible for angiogenesis and CNV membrane formation [9]. Over the recent past, neovascular AMD was treated by numerous therapeutic anti-VEGF agents, including intravitreal injections of pegaptanib sodium, bevacizumab, ranibizumab and aflibercept [10,11].

The therapeutic use of corticosteroids for inflammatory eye diseases was first described in 1951 [11]. Intravitreal corticosteroid injections have been shown to inhibit VEGF production and CNV membrane formation in animal models [12,13].

In this retrospective study, patients with neovascular AMD received combined treatment of anti-VEGF and corticosteroid or anti-VEGF monotherapy. Group A received bevacizumab and dexamethasone sodium phosphate (DSP), while Group B was treated with ranibizumab.

Bevacizumab is a full-length monoclonal antibody that is capable of binding all isoforms of VEGF. Off-label intravitreal injections of bevacizumab for neovascular AMD was first documented in 2005 [10].

Ranibizumab is an antibody fragment which also binds all isoforms of VEGF and was developed on the hypothesis that a full-size anti-VEGF antibody, such as bevacizumab, might not penetrate through the retina after intravitreal injection [14]. According to later studies, the full-length antibody bevacizumab has proved capable of penetrating

the retina in animal models [15,16], however ranibizumab appears to have an improved affinity for VEGF, compared to bevacizumab [17].

Intravitreal corticosteroids, triamcinolone and DSP in particular, have been used as adjunctive off-label treatment both with photodynamic therapy and anti-VEGF agents [18,19]. Combined treatment (Corticosteroids plus anti-VEGF), aiming at multiple components of the disease may be effective in controlling the disease progression and restoring the visual acuity in neovascular AMD [20-23].

The real challenge is to break the vicious pathophysiologic cycle that leads to AMD progression, by effectively targeting the two most significant implicated components: inflammation and VEGF.

Methods

This is a 12-month retrospective case series analysis of consecutive patients with neovascular AMD treated at the Athens Naval Hospital. The study protocol was approved by the scientific and research ethics committee of Naval Hospital of Athens (Prot. N. 7/15, Study N. 35. December 10, 2015). The purpose of the study is to determine whether combined bevacizumab plus dexamethsone reduces the number of injections required, improves BCVA and improves central macular thickness in relation to ranibizumab monotherapy. All patients had been informed about the procedure and provided signed consent before initiation of treatment.

We retrospectively identified in our written medical records all patients in which combined or monotherapy treatment was initiated for newly diagnosed treatment naïve neovascular AMD. A total of 95 newly diagnosed and AMD treatment-naïve eyes meeting the eligibility criteria were compiled retrospectively (Table 1). Group A (combination therapy) consisted of 49 eyes which received intravitreal bevacizumab (1.25 mg [0.05 mL]) and DSP (0.2 mg [0.05 mL]). Group A data was collected between 01.02.2014 and 31.10.2015. Group B (monotherapy) consisted of 46 eyes which received intravitreal ranibizumab (0.5 mg [0.05 mL]). Group B data was collected between 01.05.2013 and 31.12.2014.

Inclusion criteria	Exclusion Criteria
Age ≥ 50 years	Glaucoma
	Cataract surgery in the study eye during follow up
	Yag capsulotomy in the study eye during follow up
Presence of neovascular AMD	Diabetic retinopathy
	Previous treatment for AMD
	History of pars plana vitrectomy
	Systemic use of corticosteroids
	Recent cerebrovascular or myocardial infarction CNV caused by other conditions other than
neovascular AMD	Active ocular infection
	Subfoveal scarring, fibrosis or atrophy

Table 1: Eligibility criteria.

The assignment of patients to each group was random since ranibizumab monotherapy or bevacizumab plus DSP combined therapy was decided at the practitioner's discretion during the first visit. Therefore, the allocation of patients was random as several practitioners were involved. There were no significant differences in baseline demographics or ophthalmic history between the 2 groups.

Patients with cataract in the study eye were not primarily excluded but 4 eyes in Group A and 3 eyes in Group B were left out because they underwent cataract surgery during the follow up. In addition, 3 eyes from Group A and 2 eyes from Group B were excluded due to YAG laser posterior capsulotomy during the follow-up. These eyes were left out to prevent BCVA improvement bias. Finally, 2 eyes from Group A and 1 eye from Group B were excluded because the patients failed to comply with the monthly visit schedule. The final population of the study consisted of 40 eyes treated with bevacizumab plus DSP and 40 eyes treated with ranibizumab.

Best-corrected visual acuity (BCVA) using a 6-m Snellen chart, intraocular pressure (IOP), slit-lamp fundus examination and central macular thickness (CMT) *via* optical coherence tomography (OCT) were recorded at the initial visit (Baseline, BSL) and at each subsequent follow-up visit. Fundus fluorescein angiography (FFA) was performed at the BSL visit.

The intravitreal injection in both groups was performed in the operating theatre under sterile conditions using a 30-gauge needle. The patient received an initial drop of lidocaine 4% onto the study eye followed by 5% povidone-iodine solution 3 minutes prior to the injection. The eyelid margins, the eyelids and the periocular skin were then washed meticulously with povidone-iodine. A sterile drape and lid speculum was set in place. Another drop of 5% povidone-iodine was applied onto the eye. The injection site was marked by a caliper (3.5 mm from the limbus in pseudophakic eyes and 4.0 mm in phakic eyes at the inferior temporal quadrant).

In Group A, 0.1 ml of bevacizumab and 0.1 ml of DSP were drawn into a 1 mL syringe. From the 0.2 ml combined mixture, a total of 0.1 ml was slowly injected at the marked site from the limbus at a 90 degree angle. In Group B a total of 0.05 mL of ranibizumab (0.5 mg)

was injected. After carefully withdrawing the needle, another drop of 5% povidone-iodine was applied and a 10-second massage of the globe was performed. The patient was promptly examined *via* indirect ophthalmoscopy to confirm the presence of spontaneous retinal venous pulsation. Topical antibiotics were prescribed qid for 4 days.

All patients of both groups were followed up at 1 month intervals. Additional injections were performed in all cases of CMT>250 μm, regardless of improvement or recurrence, compared to the previous month visit. Recurrence was defined as an increase of macular edema, subretinal or intraretinal fluid with or without the presence of retinal pigment epithelial detachment as determined by OCT or by the presence of macular hemorrhage *via* slit lamp examination. Thus, the decision of PRN was based on these criteria.

BCVA was measured using a Snellen chart and converted to logMAR scale for the purpose of data analyses (Table 2). OCT scan (Stratus III OCT, Carl Zeiss) was used to evaluate CMT.

Results

Of the eighty patients (50 men, 30 women) studied, the mean age of patients in Group A was 76.97 years (range 54-91, SD 7.329) and 75.23 years in Group B (range 57-85, SD 6.834).

Fourty seven eyes were pseudophakic (26 in Group A, 21 in Group B) while 33 where phakic (14 in Group A, 19 in Group B). None of the patients had received previous therapy, all being treatment naïve for the disease.

All patients received an intravitreal injection at day 0. Group A followed a PRN scheme directly after the initial injection, while Group B received 2 additional monthly injections according to ranibizumab protocol (Preloading phase) followed by PRN scheme.

1.3	6/120
1.2	6/96
1.1	6/75
1.0	6/60
0.9	6/48
0.8	6/37
0.7	6/30
0.6	6/24
0.5	6/19
0.4	6/15
0.3	6/12
0.2	6/9
0.1	6/7
0.0	6/6
-0.1	6/5
-0.2	6/4
-0.3	6/3

Table 2: Conversion table for logmar to snellen's equivalent.

Group	BSL Inj	1 m Inj	2 m Inj	3 m Inj	4 m Inj	5 m Inj	6 m Inj	7 m Inj	8 m Inj	9 m Inj	10 m Inj	11 m Inj	Total Inj
A	40	21	19	16	22	14	14	28	18	14	18	24	248
B	40	40	40	17	23	23	22	20	26	25	18	19	313
Group A : Bevacizumab + DSP Group B : Ranibizumab													

Table 3: Number of injections per month in the 2 groups.

A total of 561 injections were performed between the two groups (Table 3). Group A received 248 injections (Mean 6.2, SD 0.966), while Group B received 313 injections (Mean 7.83, SD 2.427).

During the first 60 days (3 visits), Group A received 80 injections while Group B received 120 injections, Group B inevitably received more injections because it followed the universal standard protocol which requires a preloading phase for ranibizumab (Table 4) . The majority of the patients in Group A (28 out of 40, 70%) needed 2 injections in this time interval, while only 6 patients (15%) received 3 injections.

Number of injections	Group A	Group B
1 inj	6 (15%)	0
2 inj	28 (70%)	0
3 inj	6 (15%)	40 (100%)
Total	80	120

Group A : Bevacizumab+DSP
Group B : Ranibizumab

Table 4: Number of Injections in the first 3 visits: Number of patients (percentage).

We shall turn our attention to the number of injections received by each group during the remaining 9 months for which both groups followed a PRN scheme. During this period Group A needed less injections than Group B. In fact Group A needed 168 injections whereas Group B required 193.

Figure 1 summarizes the number of injections per month in both groups. Throughout the study (exception made for the 7th and 11th month), Group A received less injections than Group B. The more intensive approach in the first 3 visits (preloading phase) of Group B does not seem to provide some advantage over Group A, which starts with a PRN scheme from BSL. In the 2 months following the preloading phase (4th and 5th visit) CMT measurements are nearly identical in the two groups. In particular, at the 4th visit (Month 3), CMT between the groups are not statistically significantly different (CMT 259.1 ± 63.9 μm in Group A, 252.3 ± 49.5 μm in Group B). CMT was also found similar at the 5th visit (CMT 279.9 ± 74.7 μm in Group A, 275.5 ± 66.2 μm in Group B). Another observation is that in these two visits following the preloading phase of Group B, the number of patients in both groups, requiring treatment, are nearly equal (16 *vs.* 17 at the 4th visit, 22 *vs.* 23 at the 5th visit, Group A *vs.* B respectively). Finally, the preloading phase of Group B seems to have no impact in the outcome of the following months, since Group A required less injections (168 *vs.* 193 in Group B) during the last 9 months where both Groups followed a PRN scheme.

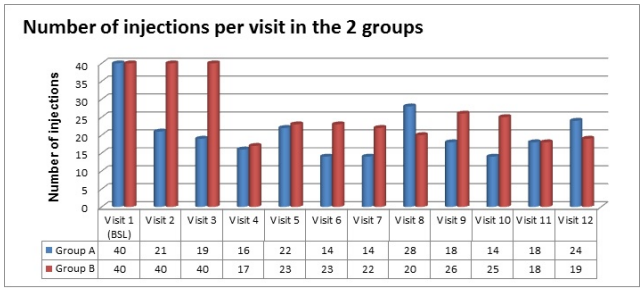

Figure 1: Number of injections per visit in the 2 groups.

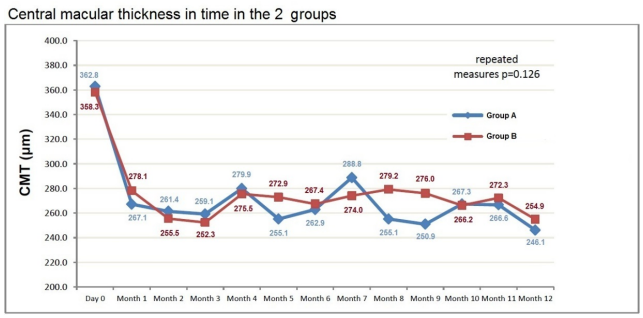

Figure 2: Central macular thickness in time in the 2 groups.

CMT at BSL was 362.8 ± 45.4 μm in Group A and 358.3 ± 47.2 μm in Group B (Figure 2). This difference is not statistically significant (p=0.649).

CMT difference between the two groups was not statistically significant throughout the study period, except month 8 (p=0,026) and 9 (p=0,015), where Group A achieved better scores. In particular, in month 8, CMT was 255.1 ± 54.8 μm in Group A and 279.2 ± 38.3 μm in Group B, likewise in month 9 CMT in Group A was 250.9 ± 41.7 μm whereas in Group B was 276 ± 48.3 μm.

In both groups, a significant reduction of CMT in the 1st month is followed by a "plateau phase" throughout the rest of the study, indicating that the initial response is highly predictive of the final outcome. In fact, after the first month CMT changes in the two groups are less significant with small trends towards improvement or recurrence. Nevertheless at the end of the 12 month period, both groups achieve slightly better scores compared to one month after the first injection.

The relative reduction of CMT is reported in Figure 3. According to the repeated measures analysis, there is not a statistically significant difference between the two groups (p=0.103) in the study period. The scores in months 8 and 9 are statistically significantly better in Group A (71.2% *vs.* 78.8% and 69.6% *vs.* 77.9% respectively).

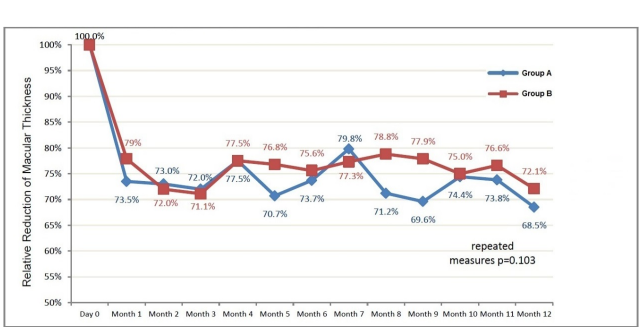

Figure 3: Relative reduction of CMT in time in the 2 groups.

BCVA at BSL was almost identical in the both groups (LogMAR 0.87 in Group A, LogMar 0.81 in Group B) (Figure 4). According to the repeated measures analysis, there is not a statistically significant difference between the two groups (p=0.006) in the study period. BCVA scores were statistically significantly better in Group A for months 5, 8 and 9 (p=0.034, 0.003 and 0.002 respectively). BCVA was improved substantially in both groups at the end of the 12 months (LogMAR 0.48 in Group A, LogMAR 0.52 in Group B).

There were no statistically significant differences between treatment groups in the measurement of IOP. IOP ranged between 12 and 21 mmHg during the study. No topical medical treatment was required in either group for IOP reduction or control. At the end of the 12 month period, IOP readings were similar, 14.9 ± 2.16 mmHg and 14.95 ± 1.96 mmHg in Group A and B respectively.

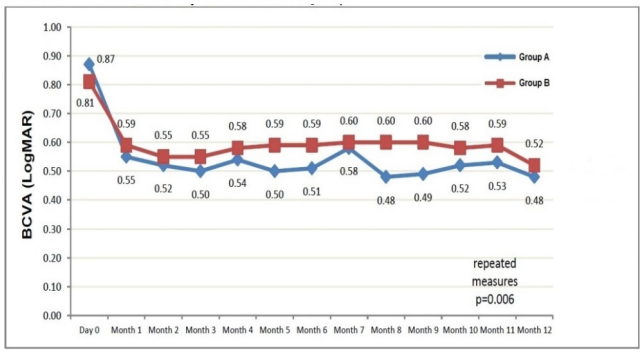

Figure 4: Best corrected visual acuity in time in the 2 groups.

Statistical methods

Summary statistics of all continuous variables were based on measures of central tendency and dispersity (mean and standard deviation) whereas categorical variables were described *via* tables of relative and absolute frequencies. The statistical evaluation of change over time regarding the macular thickness and the visual acuity was assessed by mixed models of repeated measures. Moreover, independent samples t-test was performed to evaluate any differences between the two groups of patients for each month separately. The level of significance was assumed at α=5% (i.e. p-values higher than 0.05 indicate statistically significant differences between the two groups). Analysis was performed using the SPSS v.20 statistical package (Chicago, Illinois).

Discussion

Background

Hypoxia is the main cause of VEGF induction in various cell types [24-26]. The human retina is a tissue of high oxygen demand, thus particularly susceptible to cellular damage mediated by reactive oxygen intermediates (ROI) [27].

Hypoxia promotes the expression of VEGF and hypoxia-inducible factor 1-alpha (HIF-1α) as found in mice lung tissue [28]. During hypoxic conditions, HIF-1α binds the regulatory region of the VEGF gene, inducing its transcription and initiating its expression [29,30]. DSP is capable of suppressing the angiogenesis through inhibition of VEGF and HIF-1α expression in hypoxic mice [31].

Both severe dry AMD and neovascular AMD are associated with inflammation and its mediators. Complement components such as C3, C5, C5b-9, CFH have been identified in drusen and AMD lesions. The strong correlation between AMD and chronic inflammation is further confirmed by the presence of a series of inflammatory agents within and around drusen deposits. These mediators include vitronectin, amyloid A/P, factor X, prothrombin and in some instances, immunoglobulin, HLA-DR and CRP [32,33]. In a series of ocular inflammatory conditions such as proliferative vitreoretinopathy and CNV, macrophages are identified in proximity of the RPE cells [34,35].

Macrophages produce angiogenic factors such as TNF-α, VEGF, IL-1, bFGF and TGF-β [36-38]. IL-1 and TNF-α in particular promote angiogenesis by inducing VEGF expression by the RPE cells [39]. Further studies correlate monocyte chemotaxis with neovascularization [40] and macrophage accumulation with the extent of angiogenesis after vascular occlusion [41].

AMD pathogenesis is multifactorial and consists of a vicious cycle, involving hypoxia, oxidative stress, inflammation, neovascularization and finally edema, leading to hypoxia aggravation. Anti-VEGF therapy aims to specifically inhibit VEGF. Corticosteroids can offer a valid adjunct to the treatment of AMD with their anti-inflammatory, anti-exudative and anti-angiogenic properties, while contributing to the prevention of the blood-retinal barrier breakdown [42].

It has been known that VEGF is the most important angiogenic regulator of CNV [43] and a prominent promoter of vascular permeability in AMD [44]. For this reason, VEGF is a key target in the treatment of AMD.

Nevertheless, the upstream inhibition of inflammatory VEGF activators such as IL-1 and TNF-α is another way to suppress VEGF production. Inflammatory agents can be considered the second target of AMD treatment and their suppression can be approached with the use of corticosteroids. The combination of substances which act through different mechanisms may improve long-term efficacy, safety and outcomes. It may also lead to a reduction of needed intravitreal injections [20-23].

The effectiveness of anti-VEGF and corticosteroid combination has been widely documented in recent AMD studies. In particular, intravitreal combination of triamcinolone and bevacizumab is highly effective in decreasing the amount of subretinal fluid, limiting neovascularization and preserving or increasing visual acuity [45]. Similar positive results were obtained in a recent study of combined intravitreal ranibizumab and DSP [46].

DSP was preferred as an agent in this study because of its high anti-inflammatory potency (Six times higher potency than triamcinolone) [47], fast bioavailability, transparency and immediate action. DSP can also access the posterior retina, from the vitreous and through the retina. This characteristic makes it highly effective in posterior eye disease therapy [48]. Furthermore, DSP results in fewer incidences of cataract formation and elevated IOP. Another interesting aspect of DSP, according to a recent study, is the capability of stabilizing bevacizumab *in vitro*. The combined molecule is more stable than bevacizumab alone [49].

Main findings

Even though CMT and BCVA scores at the end of the 12 month study period were similar in the two groups, Group A enjoyed a longer treatment free period than Group B (Table 5). This may be attributed to the effect of DSP. Adjunctive treatment with DSP significantly delayed the first PRN injection of bevacizumab and significantly reduced the need for repeated treatment. This difference is statistically significant, and possibly attributable to DSP action suppressing VEGF expression by upstream inhibition of inflammatory molecules. VEGF production is inhibited both directly, by the anti-VEGF antibody, and indirectly by the anti-inflammatory action of DSP.

The percentage of patients, who received treatment each month, is shown in Figure 5. The number of patients who received an injection was lower in Group A at all times, except 7th and 11th month. One can assume that the action of DSP prolonged the treatment interval thus the number of patients requiring an injection was lower in Group A. The recent findings of the CATT study in which the effect of

bevacizumab and ranibizumab are not statistically significantly different make the assumption in favor of DSP more plausible. Furthermore, the pharmacologic effect of DSP would inevitably decrease; hence the percentage of patients requiring treatment was greater in the 7th and 11th month.

	1 month free	2 months free	3 months free	4 months free	5 months free	Total
Group A	114	42	7	2	1	232
Group B	72	30	6	3	1	167
Group A : Bevacizumab + DSP, Group B : Ranibizumab						

Table 5: Consecutive Injection-free months in the two groups.

However, an acknowledged limitation relating to the need for fewer injections in Group A is the ranibizumab protocol which requires a preloading initial phase of three monthly consecutive injections. Nevertheless, in the last 9 months, were both groups are following a PRN protocol, the outcomes are nearly equal plus Group A benefits from the lower number of injections (168 *vs.* 193), compared to Group B.

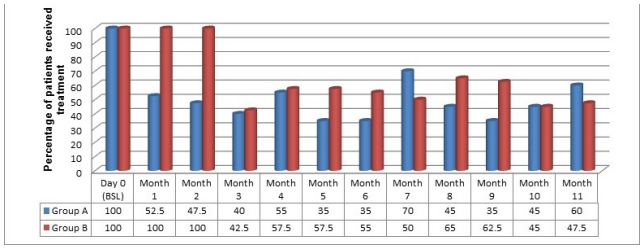

Figure 5: Percentage of patients received treatment in time in the 2 groups.

The percentage of patients who receive treatment during months 3 and 4 despite the effect of the loading dose in group B is nearly equal (40% *vs.* 42.5% for month 3, 55% *vs.* 57.5% for month 4).

CMT is also comparable between the 2 groups Similar CMT is noted in months 2, 3, 4, 6, 10, 11 and 12. Combined bevacizumab and DSP is better in months 5, 8, and 9 ranibizumab is better only in month 7.

This variability might depend on the fact that group A patients needed less injections, thus relapsed fewer times and consequently developed central macular edema (CME) for a shorter period. This difference between the two groups is documented in Table 5, taking in consideration the number of consecutive months that no treatment was needed in all patients (injection-free months) for the 12 month period. Group A achieved better scores compared to group B. In particular Group A had 114 cases of 1 injection-free month *vs.* 72 cases in Group B. In addition, Group A had 42 cases of 2 injection-free months *vs.* 30 cases in Group B.

BCVA scores in Group A were better, but the difference was not statistically significant compared to Group B. BCVA measurement is not considered a reliable method to evaluate the progression of the disease and the efficacy of the treatment. Visual acuity relies partially on a variety of factors such as fatigue, psychological state, level of attention, mental state, refractive anomalies, corneal abnormalities and underlying competitiveness. All these factors potentially introduce errors and cannot be controlled. Studies have shown that up to 13% of patients can display a 2-line discrepancy on sequential tests with a Snellen chart [50-52]. For all these reasons, CMT reduction was our main objective, and not visual acuity.

Implications for practice

The aforementioned results indicate that a combined bevacizumab and DSP PRN scheme from BSL is a valid alternative to a ranibizumab preloading phase scheme. In our case series analysis, combined bevacizumab and DSP resulted in a reduced number of injections over the 12 month treatment period. Reducing the overall number of injections is particularly important for a variety of reasons. Future routine visits for clinical assessment and the potential need for injections may in fact impose an important drain on both patients and ophthalmologists. Furthermore, the adverse effects following an intravitreal injection can be devastating. The incidence of infectious endophthalmitis according to studies, varies from 0.019 to 1.6% [53,54]. Other adverse effects include sterile intraocular inflammation, rhegmatogenous retinal detachment, intraocular or subconjunctival hemorrhage and IOP elevation. Reducing the number of injections is of imperative importance for the safety of patients and treatment, the cost-effectiveness of the treatment and the need for further appointments. The administrative process is also considerable and understandably imperative if applied on a large scale basis.

Further notes of interest

The injections in Group A were well tolerated. Increased IOP is a well-described side effect of intravitreal corticosteroid treatment [55,56]. None of the patients, phakic or pseudophakic, manifested an excessive elevation of IOP during the treatment. IOP ranged between 12 and 21 mmHg and therefore no medical intervention was needed. This could be attributed to the rapid action, short duration and clearance of dexamethasone in the vitreous [57]. Intravitreal DSP in doses up to 0.8 mg has been used for treating endophthalmitis and as complementary treatment during vitrectomy in diabetic patients, without any relevant ocular toxicity [58]. The DSP dose in this study was 0.2 mg.

In the current study none of the phakic patients presented a development or deterioration of pre-existing cataract. The task of cataract grading was assigned to the same ophthalmologist in order to ensure the minimum amount of bias. The WHO/PBD simplified cataract grading system was preferred over LOC III, since detailed description and development of cataract was not the main target of this study.

There were no incidents of ocular or systemic adverse effects, attributable to the intravitreal injection procedure, or the substances administered, such as vitreous hemorrhage, retinal tear or detachment, allergy, cataract and infection.

Intravitreal injections of anti-VEGF agents have generally been associated with fewer ocular complications than intravitreal corticosteroid injections. However, monthly treatment with anti-VEGF agents may be associated with an increased risk of cerebrovascular incidents [59,60]. In our study none of the patients presented such adverse effects, probably due to the small number of subjects participating. However, the use of an adjunctive treatment such as DSP, that would allow reduced frequency of anti-VEGF injections, may be associated with improved safety in large patient populations.

Conclusion

In summary, the results of this retrospective study demonstrate that DSP has the potential to influence the administration regimen of anti-VEGF agents in neovascular AMD patients. Combination treatment with DSP and bevacizumab provided the same efficacy and allowed a statistically significant reduction in the frequency of injections compared with ranibizumab used alone. DSP seems to prolong the beneficial effect of the anti-VEGF agent.

The anti-inflammatory action of DSP and its ability to stabilize bevacizumab *in vitro* may be some of the mechanisms involved. The retrospective nature of this study and the small patient number are aknowledged limitations, nevertheless the results are encouraging. Additional studies in a larger scale will be needed to further define the role of DSP and develop new algorithms for the treatment of neovascular ocular disease.

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