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Intravitreal Ranibizumab and Bevacizumab in Combination with Full-Fluence Verteporfin Therapy and Dexamethasone for Exudative Age-Related Macular Degeneration

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Key Words
Anti-vascular-endothelial-growth-factor antibody · Foveal thickness · Optical coherence tomography · Retreatment · Triple therapy

Abstract
Purpose: To evaluate the efficacy and safety of triple therapy with intravitreal anti-vascular-endothelial-growth-factor (VEGF) antibody, dexamethasone and verteporfin photodynamic therapy (PDT) for exudative age-related macular degeneration (AMD). ***Methods:*** Retrospective, comparative, interventional study. Records of treatment-naïve patients who received intravitreal bevacizumab or ranibizumab in monotherapy or in combination with dexamethasone and full-fluence verteporfin PDT in triple therapy were reviewed. logMAR visual acuity, foveal thickness (FT) on optical coherence tomography, intraocular pressure and endophthalmitis occurrence were recorded. ***Results:*** Sixty-one eyes were included in the triple-therapy group, 40 eyes were included in the monotherapy group. The mean follow-up was 14.1 ± 3.4 months in the triple-therapy group and 16.3 ± 4.1 months in the monotherapy group. The triple-therapy group enjoyed a lower total number of treatments (1.92 ± 0.44 vs. 3.12 ± 0.37, $p < 0.001$) and a longer time before first retreatment (5.4 ± 3.3 vs. 3.6 ± 2.5 months, $p = 0.001$). A significant improvement of visual acuity and FT was present in both groups during the 12 months following first treatment. No adverse effects were observed. ***Conclusion:*** The combination of intravitreal bevacizumab or ranibizumab with dexamethasone and full-fluence PDT for exudative AMD provided visual and anatomic improvement and a good safety profile. Triple therapy may reduce the number of retreatments when compared to anti-VEGF alone.

Introduction

In past years photodynamic therapy (PDT) with verteporfin has shown to be effective for treatment of choroidal neovascularization (CNV) in age-related macular degeneration (AMD) [1, 2]. Nevertheless, most cases require retreatment [3, 4], and reported benefits are a reduced risk of visual loss, rather than an improvement of best-corrected visual acuity (BCVA) [5]. Recently approved anti-vascular-endothelial-growth-factor (VEGF) antibodies have shown to be effective in the treatment of CNV by determining an average increase in BCVA. Ranibizumab is the antigen-binding fragment of a recombinant humanized monoclonal antibody which presents a high affinity for and inhibits the activity of all active

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forms of VEGF-A [6, 7]. Several reports have described the good safety and efficacy of intravitreal bevacizumab, an anti-VEGF monoclonal antibody approved for the intravenous treatment of metastatic cancer [8–10], which binds to all isoforms of VEGF and is still used today in this off-label indication because its cost is considerably lower than that of ranibizumab [11]. However, treatment with anti-VEGF agents often requires intravitreal injections at regular 4- to 6-week intervals, requiring frequent follow-up visits and repeated exposure to the risk of endophthalmitis [8, 10, 12, 13]. The association between the direct angio-occlusive effect of verteporfin PDT with the anti-inflammatory effect of intravitreal dexamethasone and anti-VEGF has been previously reported [14, 15]. However, only bevacizumab was administered, a reduced dose of verteporfin PDT was used, and no comparison with anti-VEGF monotherapy was done. Herein, we compared anti-VEGF monotherapy and triple therapy with bevacizumab or ranibizumab in combination with dexamethasone and full-fluence verteporfin PDT in treatment-naïve patients with exudative AMD.

Methods

The study followed the tenets of the Declaration of Helsinki and had Institutional Research Board approval. It was performed with informed consent and following all the guidelines required by the Ethics Committee.

Medical records for consecutive patients with exudative AMD treated with intravitreal anti-VEGF in monotherapy or in combination with dexamethasone and full-fluence PDT at the Eye Department of the University Hospital of Limoges from June 2006 to May 2009 were retrospectively identified. Inclusion criteria were subfoveal CNV due to AMD and no history of previous treatment in the studied eye. There was no restriction as to the type of CNV (predominantly classic, minimally classic or occult). Exclusion criteria were myopic degeneration, angioid streaks, presumed ocular histoplasmosis, retinal angiomatous proliferation or polypoidal choroidal vasculopathy, uncontrolled hypertension, recent myocardial infarction or cerebral vascular accident.

At baseline and at each following visit, Early Treatment Diabetic Retinopathy Study logMAR BCVA testing, slitlamp examination of the anterior segment, intraocular pressure measurement and dilated fundus examination were performed. Mean thickness in the central 1,000-μm diameter area (foveal thickness, FT) was measured using optical coherence tomography (Stratus OCT, version 4.0.1, Carl Zeiss Meditec, Dublin, Calif., USA). A high-resolution radial line scan protocol (1.0 B scans/s, 512 axial measurements with a resolution of around 10 μm) was used. On each follow-up visit, possible side effects of the treatment (intraocular pressure ≥23 mm Hg, anterior chamber reaction, severe lens opacity, vitreous hemorrhage, endophthalmitis, retinal detachment, significant blood pressure increase, thromboembolic events) were ruled out.

Surgical Procedure

Patients treated with monotherapy received intravitreal bevacizumab (0.05 ml solution prepared from Avastin 100 mg/4-ml vial; Roche, Switzerland) or ranibizumab (0.05 ml of 0.5 mg Lucentis, Novartis AG, Basel, Switzerland) through the pars plana according to standard procedures [16]. Patients treated with triple therapy received full-fluence PDT with verteporfin (Visudyne; Novartis) as follows: a 10-min infusion of verteporfin (6 mg/m^2 body surface area) followed by activation 5 min later by a 689-nm diode laser delivering energy of 50 J/cm^2 at an intensity of 600 mW/cm^2 for 83 s using a spot size of a diameter 1.000 μm larger than the greatest linear dimension of the lesion. An intravitreal injection of bevacizumab or ranibizumab followed by an intravitreal injection of dexamethasone (0.1 ml of 0.4 mg, Merck Génériques, France) were given within a mean of 16 h after PDT (±1 h), as previously suggested [14]. Direct light exposure of the treated eye was avoided. All injections were administered in the operating room with topical anesthesia (Tetracaine, Novartis).

Patients were observed according to the physician's discretion, at 1- to 2-month intervals. Criteria for retreatment were presence of vascular leakage on angiography or intraretinal fluid or subretinal fluid at optical coherence tomography examination. Total follow-up, total number of treatments, number of treatments per month (total number of treatments/total follow-up) and mean disease-free time (time before second retreatment) in the 2 groups were evaluated.

Statistics

Statistical analysis was performed using the Statistical Package for Social Sciences (version 17.0, SPSS Inc., Chicago, Ill., USA). The Student t test and Yates corrected χ^2 test were used for intergroup comparisons. The Kaplan-Meier method was used to estimate the retreatment-free time. Intragroup changes were compared by repeated-measures ANOVA with Dunnett correction for multiple comparisons. The level of statistical significance was set at $p < 0.05$.

Results

Sixty-one eyes (56 patients) had been treated with triple therapy. Of them, 35 had been treated with ranibizumab, and 26 had been treated with bevacizumab. Forty eyes (40 patients) had been treated with monotherapy. Of them, 18 had been treated with ranibizumab and 22 had been treated with bevacizumab. Baseline characteristics of the study groups are resumed in table 1. Nineteen cases of occult CNVs and 42 cases of classic CNVs were present in the triple-therapy group, while 13 cases of occult CNVs and 27 cases of classic CNVs were present in the monotherapy group. No significant differences were present at baseline between the triple-therapy group and the monotherapy group regarding age, BCVA and FT.

No adverse effect was noted during follow-up in any of the study groups. During the 12 months after the first

Table 1. Baseline characteristics (means ± SD) of the evaluated groups

Treatment	Eyes/ patients	Sex	Anti-VEGF, n	Age, years	CNV characteristics occult/classic, n
TT	61/56	22 M/34 F	35 TTL/26 TTA	77.2 ± 7.7	19/42 (31.1/68.9%)
MT	40/40	11 M/19 F	13 ML/17 MA	76.3 ± 8.1	13/27 (32.5/67.5%)

TT = Eyes treated with triple therapy; MT = eyes treated with monotherapy; TTL = triple therapy with ranibizumab; TTA = triple therapy with bevacizumab; ML = monotherapy with ranibizumab; MA = monotherapy with bevacizumab.

Table 2. BCVA (Early Treatment Diabetic Retinopathy Study logMAR, means ± standard deviation) and FT (μm, means ± standard deviation) at optical coherence tomography in the 2 groups at baseline and during 12 months from first treatment

	Baseline	Month 1	Month 2	Month 3	Month 6	Month 12
TT BCVA	0.94 ± 0.44	0.73 ± 0.35 (p = 0.008)	0.65 ± 0.38 (p = 0.011)	0.64 ± 0.25 (p = 0.011)	0.73 ± 0.37 (p = 0.009)	0.78 ± 0.53 (p = 0.02)
MT BCVA	1.09 ± 0.38	0.85 ± 0.42 (p = 0.009)	0.95 ± 0.38 (p = 0.011)	0.95 ± 0.46 (p = 0.008)	0.98 ± 0.42 (p = 0.009)	0.99 ± 0.37 (p = 0.03)
TT FT	323 ± 94.2	215.3 ± 57 (p = 0.001)	220.5 ± 61.6 (p = 0.03)	208 ± 37.3 (p = 0.02)	209.3 ± 47 (p = 0.02)	212.2 ± 65.3 (p < 0.001)
MT FT	384.1 ± 97.2	243.3 ± 47.6 (p = 0.011)	271.3 ± 28.3 (p = 0.011)	192.24 ± 65.5 (p < 0.001)	203.3 ± 49 (p < 0.001)	218.3 ± 61.2 (p < 0.001)

p value: significance when compared to baseline. TT = Eyes treated with triple therapy; MT = eyes treated with monotherapy.

Table 3. Mean follow-up, total number of treatments, number of treatments per month and time before retreatment in the study groups

	n	Follow-up, months	Treatments	Treatments per month	Time before retreatment, months
TT	61	14.1 ± 3.4 (1–26)	1.92 ± 0.44 (1–4)	0.13 ± 0.07 (0.07–1)	5.4 ± 3.3 (1–14)
MT	40	16.3 ± 4.1 (1–27)	3.12 ± 0.37 (1–7)	0.19 ± 0.15 (0.06–1)	3.6 ± 2.5 (1–12)

Means ± SD, ranges in parentheses; TT = all eyes treated with triple therapy; MT = all eyes treated with monotherapy.

treatment, a significant improvement of BCVA when compared to baseline was present in both triple-therapy and monotherapy groups without significant intergroup differences (table 2). In the triple-therapy group, improvement during the first 12 months was constant, while in the monotherapy group it was more pronounced during the first month. A progressive significant improvement of FT was present in both groups. The eyes with occult CNV showed a trend toward BCVA and FT improvement during the 12 months following the first treatment, although changes did not reach significance.

No significant difference as concerns the length of follow-up was present between the 2 groups (triple therapy 14 ± 3.4 months vs. monotherapy 16.3 ± 4.1 months, p = 0.09; table 3). The triple-therapy group showed a significantly lower total number of treatments during follow-up (1.92 ± 0.44 vs. 3.12 ± 0.37, $p < 0.001$), a significantly lower number of treatments per month (0.13 ± 0.07 vs. 0.19 ± 0.15, p = 0.001) and a significantly longer time before first retreatment (5.4 ± 3.3 vs. 3.6 ± 2.5 months, p = 0.001; table 3). In all cases retreatment had been performed with the same modality as at baseline.

Subgroup Analysis

During the 12 months after the first treatment, a non-significant improvement of BCVA and FT was present in the eyes treated with bevacizumab in triple therapy or monotherapy and in the eyes treated with ranibizumab

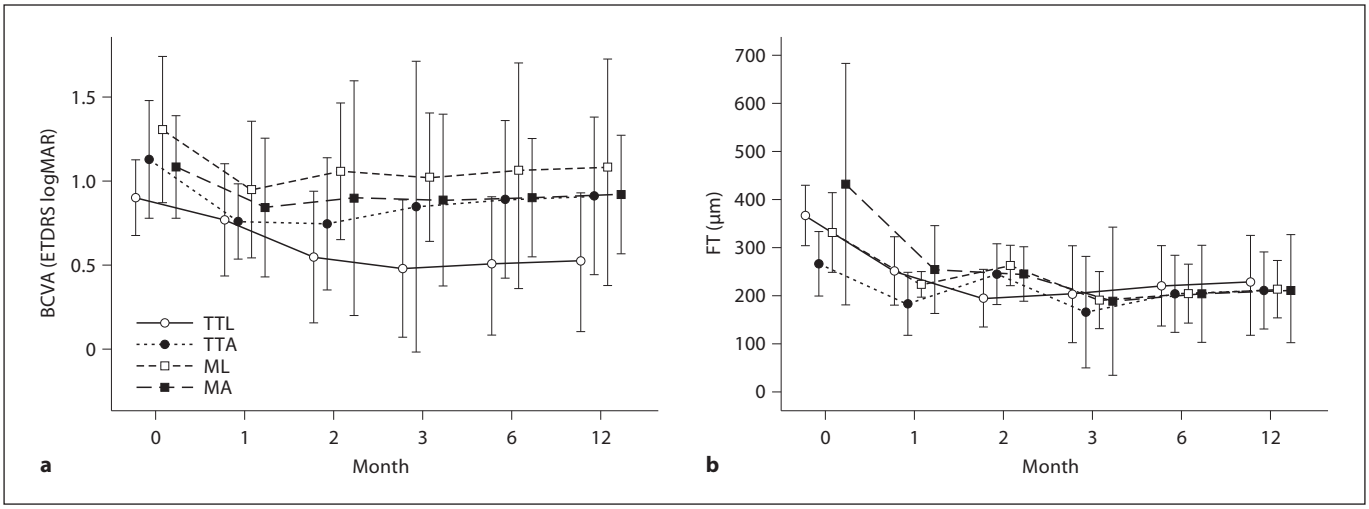

Fig. 1. Changes of BCVA (**a**) and FT (**b**) over 12 months in the 4 subgroups (means and 95% confidence intervals). TTL = Triple therapy with ranibizumab; TTA = triple therapy with bevacizumab; ML = monotherapy with ranibizumab; MA = monotherapy with bevacizumab; ETDRS = Early Treatment Diabetic Retinopathy Study.

in triple therapy or monotherapy (fig. 1), without significant intergroup differences. No significant difference was found among the 4 subgroups as concerns the number of treatments during follow-up, the number of treatments per month and time before retreatment.

Discussion

To our knowledge, this is the first study comparing ranibizumab or bevacizumab in monotherapy and in triple therapy in combination with full-fluence PDT and intravitreal dexamethasone for the treatment of exudative AMD. The combination between intravitreal bevacizumab, reduced-fluence PDT and intravitreal dexamethasone [14, 15], and the combination between standard fluence PDT, bevacizumab and intravitreal triamcinolone [17, 18] have previously been shown to determine a sustained improvement of both BCVA and FT with a reduced number of injections, although no monotherapy group was used for comparison.

A significant improvement of BCVA and FT was present in both monotherapy and triple-therapy groups, without significant intergroup differences. PDT acts by determining a direct closure of neovascular membranes, but initiates an inflammatory response and upregulates VEGF and other growth factors [19]. Anti-VEGF therapy targets key mediators of the angiogenic cascade resulting in suppression of activity of choroidal neovascular lesions due to AMD. Therefore, in combination treatment, PDT directly destroys existing CNVs while anti-VEGF drugs prevent their further growth and limit the inflammatory effects of PDT. A combination therapy of PDT with anti-angiogenic agents has been shown to be effective in neovascular AMD, especially by prolonging the intervals for reinjections [20, 21]. The anti-inflammatory properties of steroids limit any further VEGF increase after PDT [14]. The combination of verteporfin with steroids such as intravitreal triamcinolone and dexamethasone has been shown to determine a visual acuity improvement with few treatments [22–29]. When compared with a suspension of triamcinolone, dexamethasone solution presents no sustained release, a more rapid clearance from the vitreous and a better safety profile as it does not determine the increase in intraocular pressure [14]. Furthermore, it has been shown to have antifibrotic, antiproliferative and antimigration properties. As previously suggested [14], we administered dexamethasone and the anti-VEGF drug 16 h after PDT in order to prevent the PDT-mediated overactivation of the inflammatory cascade without blocking the therapeutic effects of PDT which depend on immunologically mediated processes.

In the triple-therapy group, a significantly lower number of treatments and a significantly longer time before retreatment were observed. Long-lasting effects are limited in PDT monotherapy due to the persisting inflammation and edema, and in anti-VEGF monotherapy due to the persistence of CNV. Both ranibizumab and be-

vacizumab treatments usually need repeated administrations to achieve and maintain positive results. Twelve-month results of the Mont Blanc prospective, randomized, double-masked, multicenter trial show that combining standard fluence PDT with ranibizumab 0.5 mg can deliver BCVA improvements that are noninferior to a ranibizumab monotherapy regimen with 3 loading doses followed by injections on a monthly as-needed basis, although no significant difference was found between the combination and monotherapy groups with regard to the proportion of patients with a treatment-free interval of at least 3 months duration after month 2 [30]. The reduced number of retreatments enjoyed by the triple therapy group in our study could be explained by the adjunct of dexamethasone, which would blunt the PDT proinflammatory effects. A combined triple therapy which allows to prolong the intervals for reinjections and to reduce the number of intravitreal injections could represent a good option in terms of durability, safety and cost.

All the eyes with occult CNV showed a trend toward visual and anatomic improvement during the first 12 months after treatment, although this was not statistically significant. In the past, PDT was considered the standard therapy for patients with predominantly classic subfoveal CNV due to neovascular AMD [31, 32]. On the other hand, our results are confirmed by the recently reported effectiveness of a combined therapy with PDT and intravitreal ranibizumab in occult CNVs [33, 34].

In this study full-fluence PDT was used, and a reduction in the number of injections was obtained, as reported in studies using reduced-fluence PDT [14, 15]. Therefore, the anti-inflammatory effect of dexamethasone probably limited the dose-related side effects of full-fluence PDT.

In both triple therapy and monotherapy groups, BCVA and FT improved not depending on whether bevacizumab or ranibizumab was used, although without significant differences. Our data agree with a recent study by Fong et al. [35], who reported a similar effectiveness of both bevacizumab and ranibizumab treatments in stabilizing BCVA loss without differences in BCVA outcome.

No complication was noted during follow-up in any of the study groups. Possible ocular complications following intravitreal injections are endophthalmitis, retinal detachment, vitreous hemorrhage and lens injury [35] while systemic adverse effects related to the anti-VEGF drug may be secondary to accelerated collateral-vessel closure like thromboembolic events [6, 36–39]. Monthly injections of anti-VEGF may increase the risk of complications. Combination therapies could represent a valid approach to reduce the number of injections.

A limitation of our study is the retrospective design. However, the population size and the 12-month follow-up may help support our findings. A prospective study is planned to confirm our results.

In conclusion, treatment of naïve patients with exudative AMD with triple therapy with bevacizumab or ranibizumab in combination with dexamethasone and verteporfin PDT provided similar visual and anatomic improvements when compared to anti-VEGF monotherapy, with a reduced number of injections and a longer time before retreatment. Clinical trials are needed to confirm our preliminary results.

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