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Intravitreal triamcinolone, bevacizumab and pegaptanib for occult choroidal neovascularization

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ABSTRACT.

Purpose: **To evaluate best-corrected visual acuity (BCVA) and foveal thickness (FT) changes in occult subfoveal choroidal neovascularization (CNV) from age-related macular degeneration (AMD) after intravitreal bevacizumab (IVB, 1.25 mg/0.05 ml), pegaptanib (IVP, 0.3 mg/0.09 ml) and triamcinolone acetonide (IVTA, 4 mg/0.1 ml) injected on an as needed basis.**

Methods: **Retrospective, interventional, comparative study. BCVA (Early Treatment Diabetic Retinopathy Study LogMAR) and FT by optical coherence tomography (OCT) were evaluated during 12 months from first treatment. Patients were retreated if signs of neovascular activity were still present on angiography or OCT.**

Results: **Forty-eight eyes received IVB, 43 eyes received IVP, 52 eyes received IVTA. BCVA and FT at baseline were 1.22 ± 0.49 LogMAR and 410.2 ± 41.83 μm in the IVB group, 1.25 ± 0.43 LogMAR and 452.3 ± 44.83 μm in the IVP group and 1.31 ± 0.4 LogMAR and 456.6 ± 48.27 μm in the IVTA group. BCVA and FT improved in the three groups during follow-up. A significantly greater improvement of BCVA was present at month-3, month-6 and at month-12 in the IVB and IVP groups ($p = 0.01$). Improvement of FT was greater in the IVTA group at month-3 ($p = 0.02$), while it was greater in the anti-Vascular Endothelial Growth Factor (VEGF) groups at month-6 and month-12 ($p = 0.01$). A postoperative increase of intraocular pressure was detected in 9/52 (17.3%) eyes treated with IVTA, and in two cases it was resistant to topical therapy.**

Conclusion: **Intravitreal injection of anti-VEGF drugs administered on an as needed basis for AMD-related occult CNVs provided functional and anatomic improvement during 12 months of follow-up.**

Key words: age-related macular degeneration – anti-VEGF – as needed treatment

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Introduction

Age-related macular degeneration (AMD) is one of the leading causes of visual impairment in Western countries (West 2000). The exudative form of AMD is associated with high levels of intravitreal Vascular Endothelial Growth Factor (VEGF). The first intravitreal drug to be used for exudative AMD was triamcinolone acetonide. Corticosteroids have been shown to inhibit VEGF production, vascular proliferation and vascular permeability (Nauck et al. 1998; Penfold et al. 2000; Ciulla et al. 2001). Intravitreal injection of triamcinolone acetonide (IVTA) results in reduction in the growth of choroidal neovascularizations (CNVs) when used as single therapy (Gillies et al. 2003; Jonas et al. 2003). Recently approved anti-VEGF antibodies have shown to be effective in the treatment of CNV because of AMD by determining an average increase of visual acuity, with a lower complication rate than triamcinolone acetonide (Browns Brown et al. 2009; Kaiser et al. 2007). Pegaptanib is an anti-VEGF RNA–based aptamer that specifically binds VEGF165 isoform (Gragoudas et al. 2004). Furthermore, several reports have described the good safety and efficacy of intravitreal bevacizumab, an anti-VEGF drug directed at all isoforms of VEGF, approved for the intravenous treatment of metastatic cancer (Michels et al. 2005; Rosenfeld et al. 2005) and still used today in this off-label indication because its cost is considerably lower than that of licensed anti-VEGF (Rosenfeld

2006). Herein, we have retrospectively evaluated patients treated with bevacizumab, pegaptanib and triamcinolone on as needed basis for occult AMD-related choroidal neovascularization.

Methods

The study was approved by the eye clinic's ethics committee. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. In a retrospective comparative study carried out at the Eye Department of the University Federico II of Naples, we considered all the eyes with occult subfoveal CNV treated with intravitreal bevacizumab, pegaptanib or triamcinolone acetonide between December 2005 and April 2008. Minimally classic CNVs, classic CNVs, retinal angiomatous proliferation and polypoidal choroidal vasculopathy were excluded by analysis of fluorescein angiography and indocyanine green angiography. Eyes with open angle glaucoma and an intraocular pressure (IOP) greater than 22 mmHg were also excluded from the study. Treatment was performed with intravitreal injection of bevacizumab, pegaptanib or triamcinolone. IVTA was administered between December 2005 and April 2006 because the use of anti-VEGF drugs for neovascular AMD was not yet widespread. Bevacizumab was administered between December 2005 and November 2007 as it was the only anti-VEGF drug available at our hospital during that period. Between December 2005 and April 2006, triamcinolone and bevacizumab were used randomly by different surgeons. Pegaptanib was administered between November 2007 and April 2008. The changeover to pegaptanib was because of its licensed status when compared to bevacizumab. When bevacizumab and triamcinolone were used for injection, each patient was informed of their off-label status and informed consent was obtained. Bevacizumab (0.05 ml solution prepared from Avastin 100 mg/4 ml vial; Roche, Switzerland), pegaptanib (0.3 mg/0.09 ml, Macugen®; Eye Tech/Pfizer, New York, NY, USA) or triamcinolone acetonide (4 mg/0.1 ml; Kenacort-A; Bristol-Myers Squibb, Sermoneta, Latina, Italy) were administered intravitreally through the pars plana according to standard procedures (Jonas et al. 2003). Patients were retreated during follow-up if vascular leakage was still present on angiography or intraretinal fluid or subretinal fluid was detected by optical coherence tomography (OCT). Bevacizumab and pegaptanib were readministered after at least 1 month from previous injection, while minimum time before retreatment for IVTA was 4 months.

Data collection included the history of any treatment for AMD in the study eye, Early Treatment Diabetic Retinopathy Study (ETDRS) LogMAR best-corrected visual acuity (BCVA) testing, slit lamp examination of the anterior segment, IOP measurement and dilated fundus examination. At each visit, mean thickness in the central 1000-μm diameter area (foveal thickness, FT) was measured using optical coherence tomography (Stratus OCT, Version 4.0.1; Carl Zeiss Meditec, Dublin, CA, USA). High-resolution Radial Line scan protocol (1.0 B scans/second, 512 axial measurements with a resolution of around 10 microns) was used. The inner and outer retinal boundaries for measurement of FT were defined automatically by the computer software. Patients were observed at baseline and monthly with retreatment based on disease activity. Fluorescein angiography and indocyanine green angiography were performed at baseline, at month-3, at month-6, at month-12 and in case of BCVA reduction. Data at baseline, month-3, month-6 and month-12 were collected. Adverse effects considered during follow-up were raised intraocular pressure, development of cataract, ocular toxicity or uveitis, retinal pigment epithelial tear, endophthalmitis, rhegmatog enous retinal detachment, systemic adverse events such as thrombosis or hypertension.

Statistical analysis was performed using the Statistical Package for Social Sciences (version 17.0; SPSS Inc., Chicago, IL, USA). Intragroup changes were compared by repeated measures ANOVA with Dunnett correction for multiple comparisons. The differences in the results between the three groups were compared by means of the Mann–Whitney *U*-test. Spearman correlation was used to evaluate correlation between anatomic and functional changes. The level of statistical significance was set at $p < 0.05$. Data are presented as means ± standard deviation.

Results

Data about characteristics of the two groups at baseline are resumed in Table 1. In the bevacizumab (IVB) group, there were 48 eyes (48 patients, 26 women, 22 men, mean age 75.5 ± 6.8 years). In the pegaptanib (IVP) group, there were 43 eyes (43 patients, 20 women, 23 men, mean age 77.2 ± 7.1 years). In the triamcinolone group, there were 52 eyes (52 patients, 27 women, 25 men, mean age 76.2 ± 5.8 years). Mean BCVA and FT were 1.22 ± 0.49 LogMAR and 410.2 ±

Table 1. Characteristics of the study groups at baseline.

	IVB	IVP	IVTA	p
n eyes (patients)	48 (48)	43 (43)	52 (52)	0.1
Male/Female (%/%)	22/26 (45.9/54.1)	23/20 (53.5/46.5)	25/27 (48.1/51.9)	0.08
Age (years, Mean ± SD)	75.5 ± 6.8	77.2 ± 7.1	76.2 ± 5.8	0.7
LogMAR BCVA (Mean ± SD)	1.22 ± 0.49	1.25 ± 0.43	1.31 ± 0.4	0.08
FT (μm, Mean ± SD)	410.2 ± 41.83	452.3 ± 44.83	456.6 ± 48.27	0.07
Previous PDT (cases)	7 (14.5%)	5 (11.6%)	9 (17.3%)	0.1
Time from last PDT (months, Mean ± SD)	6.2 ± 3.2	5.3 ± 2.1	6.8 ± 2.2	0.1

IVB = intravitreal bevacizumab; IVP = intravitreal pegaptanib; IVTA = intravitreal triamcinolone; SD = standard deviation; BCVA = best-corrected visual acuity; FT = foveal thickness; μm = microns; PDT = photodynamic therapy.

41.83 μm in the IVB group, 1.25 ± 0.43 LogMAR and 452.3 ± 44.83 μm in the IVP group, 1.31 ± 0.4 LogMAR and 456.6 ± 48.27 μm in the IVTA group. No significant differences were present at baseline among the three groups as concerns number of eyes, age, BCVA and FT.

Full fluence photodynamic therapy (PDT) had been administered in seven cases (14.5%) 6.2 ± 3.2 months prior to IVB, in five cases (11.6%) 5.3 ± 2.1 months before IVP and in nine cases (17.3%) 6.8 ± 2.2 months before IVTA. No difference as concerns the number of PDT treatments prior to anti-VEGF treatment ($p = 0.01$) and time from last PDT treatment ($p = 0.01$) was present among the three groups.

Mean number of injections during 12 months after first treatment was 4.3 ± 0.4 in the IVB group, 4.1 ± 0.2 in the IVP group and 3.2 ± 0.2 in the IVTA group. All patients completed the 12 months follow-up. During follow-up, no patient was treated with drugs other than the one used for the initial treatment. No significant differences were present between the IVB and the IVP groups as concerns the number of injections, while the number of injections in the IVTA group was significantly lower ($p = 0.02$) because of the longer time before retreatment in this group.

A significant improvement of BCVA was present in the bevacizumab group and in the pegaptanib group at month-3 (0.81 ± 0.3 LogMAR, $p = 0.05$ and 0.80 ± 0.44 LogMAR, $p = 0.04$, respectively), month-6 (0.61 ± 0.21LogMAR, $p = 0.005$ and 0.81 ± 0.43 LogMAR, $p = 0.03$, respectively) and month-12 (0.65 ± 0.4 LogMAR, $p = 0.005$ and 0.83 ± 0.44 LogMAR, $p = 0.03$, respectively) (Fig. 1). In the IVTA group, a nonsignificant improvement of BCVA was present at month-3 (1.20 ± 0.11 LogMAR, $p = 0.2$), month-6 (1.03 ± 0.29 LogMAR, $p = 0.07$) and month-12 (1.08 ± 0.32 LogMAR, $p = 0.08$). In the IVB and in the IVP group, no patient showed a worsening in BCVA, while in the triamcinolone group 8/52 patients (15.3%) experienced a visual loss of 0.2 ± 0.09 LogMAR at month-3, 0.17 ± 0.07 LogMAR at month-6 and 0.19 ± 0.08 LogMAR at month-12. At month-3, month-6 and month-12 improvement in BCVA was significantly greater after IVB than after IVTA ($p = 0.01$), as was greater after IVP than after IVTA ($p = 0.01$). No significant differences in BCVA change were present after IVB and IVP at month-3 ($p = 0.08$), month-6 ($p = 0.07$) and month-12 ($p = 0.07$). No significant differences in BCVA change were present between eyes with prior PDT and treatment-naïve eyes.

As concerns FT, a significant improvement was present in both IVB and IVP groups at month-3 (316.2 ± 25.16, $p < 0.001$ and 340.4 ± 10.70, $p < 0.001$, respectively), month-6 (230.2 ± 11, $p < 0.001$ and 264.5 ± 12.35, $p < 0.001$, respectively) and month-12 (233.1 ± 18, $p < 0.001$ and 274.3 ± 13.33, $p < 0.001$, respectively) (Fig. 1). The IVTA group showed an improvement that was significant at month-3 (248.3 ± 26.20, $p = 0.005$), but not at month-6 (398.7 ± 36.74, $p = 0.1$) and at month-12 (373.5 ± 28.22, $p = 0.1$). At month-3, the FT improvement in the IVTA group (−45.6%) was greater than in the IVB and IVP groups (−22.9% and −24.7, respectively) ($p = 0.02$). At month-6 and at month-12, the anti-VEGF groups experienced a significantly greater improvement of FT ($p = 0.01$). Correlation between BCVA and FT change was 0.33 (Spearman rho, $p = 0.001$) in IVB group, 0.26 in IVP group ($p = 0.02$) and 0.31 ($p = 0.001$) in the IVTA group. Eyes with prior PDT did not significantly differ from treatment-naïve eyes as concerns FT.

A detachment of the pigment epithelium was present at baseline in 21/48 (43.7%) eyes treated with bevacizumab, in 17/43 (39.5%) eyes treated with pegaptanib and in 30/52 (57.6%) eyes treated with triamcinolone. IVB lead to resolution of the PED in 8/21 (38%) eyes and was more effective than IVP (5/17 cases, 29.4%, $p = 0.005$) and IVTA (6/30 eyes, 20%, $p < 0.001$). Also IVP was significantly more effective than IVTA ($p < 0.001$). No tears of the pigment epithelium were detected in any group during follow-up. Among cases

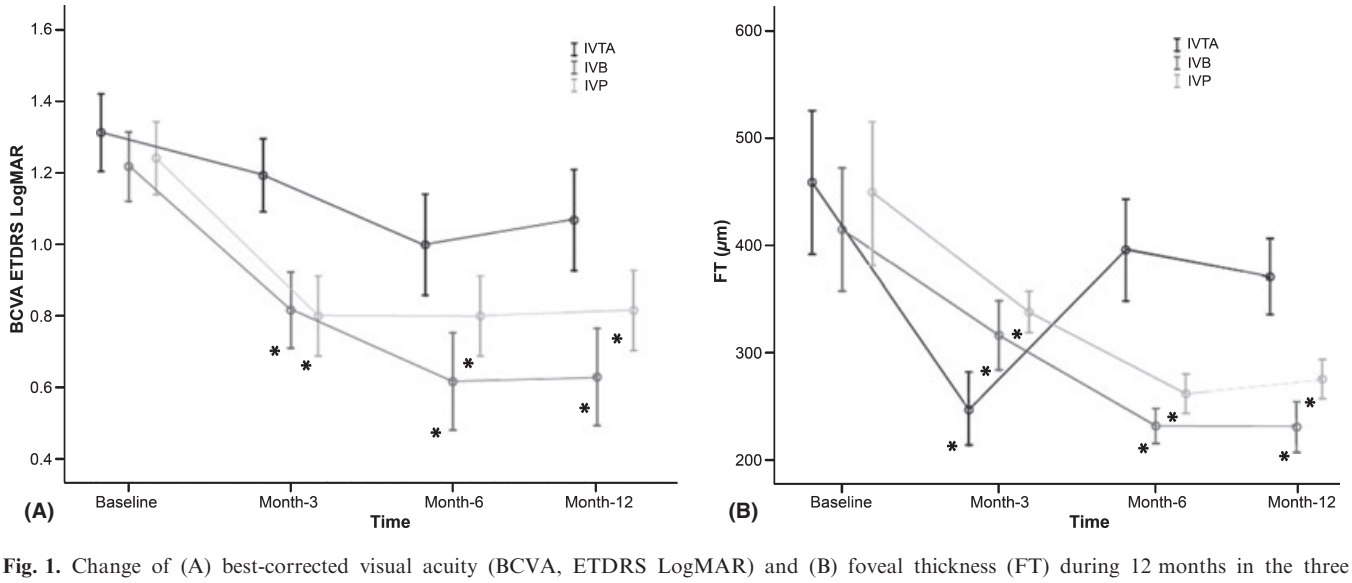

Fig. 1. Change of (A) best-corrected visual acuity (BCVA, ETDRS LogMAR) and (B) foveal thickness (FT) during 12 months in the three groups (means and 95% confidence interval). IVTA = intravitreal triamcinolone acetonide; IVB = intravitreal bevacizumab; IVP = intravitreal pegaptanib; *$p < 0.05$.

with PED at baseline, visual acuity at 12-month visit had improved in 12/68 cases (17.6%), was stable in 43/68 cases (63.2%) and worsened in 13/68 eyes (19.1%).

A reduction of the intraretinal oedema and subretinal fluid was present in the three groups. Although reduced, after 3 months subretinal fluid was still persistent in 12/52 (23%) eyes treated with IVTA, in 11/48 (22.9%) eyes treated with IVB and in 11/43 (25.5%) eyes treated with IVP. After 6 months, subretinal fluid was persistent in 27/52 (51.9%) eyes treated with IVTA, in 6/48 (12.5%) eyes treated with IVB and in 7/43 (16.2%) eyes treated with IVP. After 12 months, subretinal fluid persisted in 16/52 (30.7%) eyes treated with IVTA, in 5/48 (10.4%) eyes treated with IVB and in 7/43 (16.2%) eyes treated with IVP.

No side-effects were present in the IVB and IVP groups. A postoperative increase of IOP >23 mmHg was detected in 9/52 (17.3%) eyes treated with IVTA. In 7/9 cases, IOP was lowered to values <21 mmHg with topical antiglaucomatous treatment after a mean period of 5.6 ± 1.4 months. In 2/9 cases, glaucoma filtration surgery was necessary to reduce IOP.

Discussion

To our knowledge, this is the first reported comparative evaluation of intravitreal injection of bevacizumab, pegaptanib and triamcinolone acetonide for AMD-related occult CNVs.

A significant improvement in BCVA was present in the IVB and IVP groups during 12 months. At 12-month visit, BCVA had improved by 0.55 LogMAR in the IVB group and by 0.42 LogMAR in the IVP group. Our results agree with the significant 0.37 LogMAR improvement in BCVA recently reported for occult CNVs during 12 months after treatment with intravitreal bevacizumab (Costagliola et al. 2009). As concerns treatment with pegaptanib, recent studies have reported a significant 0.10 LogMAR improvement after 9.1 months (Quiram et al. 2007) and a significant 0.28 LogMAR improvement after 12 months (Sivaprasad et al. 2008). In the IVTA group, a BCVA improvement was present, but not significant. In the IVTA group, the improvement of FT at month-3 was statistically greater, while at month-6 and month-12 only the anti-VEGF groups showed a persistent and significant improvement. The effectiveness of intravitreal triamcinolone in reducing retinal oedema has been previously reported (Steen et al. 1998; Jonas & Sofker 2001; Sutter et al. 2004), but no beneficial effect have been shown on eyes with minimally classic or occult CNV secondary to AMD (Jonas et al. 2006; Lee et al. 2007). The differences in visual outcome between eyes treated with triamcinolone and eyes treated with anti-VEGF drugs may be explained by the fact that anti-VEGF drugs have a stronger anti-angiogenic effect than IVTA (Jonas et al. 2009). The low correlation found in our study between anatomic and functional effects of IVTA during follow-up agrees with previously reported studies about the use of IVTA in exudative AMD (Gillies & Larsson 2007) and diabetic retinopathy (Larsson et al. 2005), and suggests a role of factors other than retinal oedema on visual recovery, such as the function of the retinal pigment epithelium and its relationship to the photoreceptors (Gillies et al. 2003).

The main anatomic effect of the three intravitreal drugs was the reduction of the intraretinal oedema, which improved in the three groups. PED persisted after treatment in most cases, while subretinal fluid improved at month-3 in the three groups and greatly worsened during following months in the IVTA group. Foveal thickness showed a greater improvement in the IVTA group at month-3, mainly because of the reduction of intraretinal oedema, although a similarly greater improvement of visual acuity was not present. The low correlation between BCVA and FT has been reported already (Spaide et al. 2006).

The resolution of the PED was obtained in 38% of the eyes treated with bevacizumab and in 29.4% of the eyes treated with pegaptanib. The low responsiveness of the PED to intravitreal anti-VEGF has been already reported (Atmani et al. 2009; Furino et al. 2009). As also suggested by our data, pegaptanib has shown less effectiveness than bevacizumab in reducing PED height in retrospective large series, probably because of its lower effectiveness in reducing vascular permeability (Lommatzsch et al. 2009). Of 68 eyes with PED at baseline, BCVA at 12-month visit only improved in 17.6% and remained stable in 63.2% of cases. These data agree with previous findings by Atmani et al. (2009), who suggested CNV lesions associated with PED to be a severe form of neovascular AMD less responsive to treatment.

No tears of the pigment epithelium were detected in any group during 12 months of follow-up. Tears of the retinal pigment epithelium have been reported after intravitreal anti-VEGF with an incidence ranging from 0.06% to 12.5% (Fung et al. 2006; Garg et al. 2008; Wong et al. 2008; Gelisken et al. 2009). The absence of such a complication in our series could be explained by the relatively short mean follow-up.

No significant difference in the number of injections was noted between the IVB and IVP groups, while comparison with the IVTA group was not possible because of the different minimum time for retreatment. Off-label use of intravitreal bevacizumab has been shown to significantly improve vision in several studies (Avery et al. 2006; Rich et al. 2006; Spaide et al. 2006). In a recent prospective study, intravitreal pegaptanib provided good long-term results in predominantly and pure occult CNVs (79% responders, 43% maintainers, and 9% gainers at 52 weeks after eight injections) (Atmani et al. 2009). In the Vascular Endothelial Growth Factor Inhibition Study in Ocular Neovascularization (VISION) trial, 6% of patients receiving pegaptanib for CNV lesions of all angiographic subtypes showed significant visual improvement compared with 2% of sham-treated controls (Gragoudas et al. 2004). Anti-VEGF agents decrease the plasma leak through incompetent neovascularization and result in a temporary increase in vision. They often require frequent intravitreal injections, which carry the risks of retinal tear and endophthalmitis (van Wijngaarden et al. 2005). In our study, retreatment was performed on an as needed basis, and an overall functional and anatomic improvement was obtained. VEGF is required for the maintenance of physiological vascular structures, and a reduction in choriocapillary fenestration was recently

reported following anti-VEGF therapy (Peters et al. 2007). A retreatment strategy based on the disease activity seems advisable to ensure that as much as needed (but as little as possible) VEGF inhibition is induced.

Although according to reported suggestions IVTA was reinjected after at least 4 months (Gillies et al. 2003), a postoperative increase in IOP was detected in nine cases treated with intravitreal triamcinolone (17.3%) and was resistant to topical antiglaucomatous treatment in two cases. The local and systemic safety of intravitreal anti-VEGF has been previously described (Aiello et al. 2004; Noma et al. 2008), while corticosteroids often determine cataract formation and elevation of IOP (Armaly 1965; Butcher et al. 1994).

In our study, no significant difference in the number of prior visudyne PDT treatments was found among the three groups. The lack of efficacy of PDT with verteporfin in patients with occult CNV lesions was recently confirmed in the Visudyne in Occult (VIO) trial (Kaiser et al. 2009), while the VISION trial demonstrated the safety and efficacy of VEGF inhibitors in all types of neovascular AMD (Gragoudas et al. 2004). However, the influence of any prior treatment on the outcome of anti-VEGF injection is controversial. As the evaluation of previously treated and treatment-naive patients showed similar outcomes in vision improvement and FT reduction (Goff et al. 2007; Leydolt et al. 2010), our results could be extended to treatment-naïve patients.

Nowadays, anti-angiogenic intravitreal treatment is a mainstay for all lesion subtypes in neovascular AMD. Combined treatment with steroids and PDT has shown promising results mostly as concerns the reduction of retreatment rates (Augustin & Schmidt-Erfurth 2006). Emerging strategies include RNA interference, anti-VEGF Trap, blockage of tyrosine kinase cascade, RPE-derived factor-based therapies, nicotinic acetylcholine receptor antagonists, immunosuppressant sirolimus and gene therapy, which are currently under study.

In conclusion, intravitreal bevacizumab, pegaptanib and triamcinolone injected on an as needed basis for AMD-related occult CNVs provided improvement of BCVA and FT during 12 months of follow-up. Better visual and anatomic outcome was observed in eyes treated with bevacizumab and pegaptanib, while IVTA was associated with a higher risk of IOP increase. Therefore, anti-VEGF drugs should be considered as a mainstay for treatment of occult CNVs, while treatment with IVTA should not be used because of its side-effects.

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