RANIBIZUMAB (LUCENTIS®) INJECTION BY ANTERIOR CHAMBER IN APHAKIC EYES WITH MYOPIC CHOROIDAL NEOVASCULARIZATION

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Purpose. macular choroidal neovascularization (CNV) is one of the most vision-threatening complications of myopia, which can lead to severe vision loss. Our purpose was to evaluate the safety and efficacy of trans-corneal injection of ranibizumab in the treatment of myopic CNV in aphakic patients.
Materials And Methods. ten eyes of 10 aphakic patients with CNV secondary to pathologic myopia treated with three trans-corneal injection of ranibizumab were evaluated. A complete ophthalmologic examination including best-corrected visual acuity (BCVA) and fundus biomicroscopy, specular microscopy, fundus optical coherence tomography (OCT), fluorescein angiography (FA) were performed at baseline and monthly for all patients. Mean time of follow-up was 6 months.
Results. The mean axial length was 27,6 mm (range, 25.7-31.3 mm). The mean initial visual acuity (VA) was 0.19 (decimal equivalent). A statistically significant improvement to a mean VA of 0.33 decimal equivalent (log-MAR:0.48) was demonstrated at the final follow-up. VA improved by a mean of 2.86 lines. Mean central macular thickness (CMT) measured with OCT was 340 µm (range, 179-663 µm) at the baseline, and was reduced significantly at the final follow-up to 212µm (range, 125-455 µm). No injection complications or drug-related side effects were noted during the follow-up period.
Conclusions. in this small series of aphakic eyes with limited follow-up, ranibizumab by anterior chamber administration seems to be a safe and effective treatment for CNV secondary to pathologic myopia (PM), without any complications. Further studies to evaluate the safety and efficacy are justified.
Keywords. Ranibizumab, safety, efficacy, myopic CNVs, aphakia, anterior chamber.

INTRODUCTION

Pathological myopia (PM) is one of the leading causes of visual disability in the world from 20–50 years of age[1,2]. Choroidal neovascularization (CNV) is one of the most important vision-threatening complications of PM and occurs in 5–10% of myopic patients, with a positive correlation between risk and degree of myopia. Among myopic patients with pre-existing CNV, more than 30% will develop CNV in the fellow eye within 8 years[3,4] .

The process of angiogenesis is multi-factorial and highly complex, but vascular endothelial growth factor (VEGF) is considered critical both in physiological and in pathological angiogenesis[5,6].

Ranibizumab (Lucentis®, Novartis, Basel, Switzerland) is an anti-VEGF antibody recommended as an option for the treatment of wet age-related macular degeneration (AMD). Usually it's inserted with intravitreal (IVT) injection via pars plana and the recommended dose is 0,5 mg (0,05 ml)[7]. Several studies have reported promising short-term results with off-label use of the intravitreal anti-VEGF drug ranibizumab for the treatment of CNV in PM[8,9,10].

The IVT injection procedure as such is not without risks for serious complications such as endophthalmitis[11,12], retinal detachment, perivenous retinal haemorrhages[13,14,15], vasculitis and increased intraocular pressure (IOP). An anterior chamber ocular inflammation is possible: it's dose-dependent, relatively rapid (peaked at day 2 post injection) and transient. In the vitreous, it was later (peaked at week 1 post injection) and more persistent[16]. Retinal detachment is more frequent in hypermyopic patients with peripheral retinal degeneration[17,18].

The purpose of this study was to evaluate safety and efficacy of trans-corneal injection of ranibizumab by anterior chamber in 10 hypermyopic and aphakic patients with CNV and with peripheral retinal degeneration or retinal tears (treated by argon laser) or previous retinal detachment in the fellow eye.

MATERIALS AND METHODS

We conducted a prospective, consecutive, non-randomized, interventional study of 10 eyes of 10 patients with CNV secondary to pathologic myopia treated with trans-corneal injection of ranibizumab in St.Maria Scotte Siena Hospital. Best-corrected visual acuity (BCVA), slit-lamp examination, specular microscopy, optical coherence tomography (OCT), and fluorescein angiography (FA) were performed at baseline and monthly for all patients.

Inclusion criteria were retinal signs of PM, 6 months of follow-up, evidence of an active CNV on the basis of the presence of leakage on fluorescein angiography (FA)and/or intra-retinal or sub-retinal fluid on optical coherence tomography (OCT); all eyes were aphakic

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and had myopic retinal abnormalities such as peripheral retinal degeneration or retinal tears (treated by argon laser). Two case showed previous retinal detachment in the fellow eye.
Patient age, sex, affected eye, spherical equivalent refraction and any previous treatment administered were recorded.
The mean age of the patients was 53 years (range, 37 - 78 years); mean time of follow-up was 6 months and the patients were followed every month. Angiographic features in all cases demonstrated active CNV and patients with active CNV secondary to PM were offered treatment with intravitreal ranibizumab in an 'off-label' fashion. The potential benefits and side effects were discussed with patients and relatives: an informed consent was obtained from all patients after a thorough discussion before each injection. The number of intravitreal injections administered for each patient was 3.
All injections were performed by the same surgeon (Esposti Pier Luigi) using the same technique. Ranibizumab 0.5 mg (0.05 ml) was administered by trans-corneal injection under sterile conditions in the operating theatre. Before injection, tetracaine 0.5% was applied topically. Povidone iodine 5% was applied to eyelid margins, eyelashes, and conjunctival surface, and a lid speculum was placed. An additional drop of povidone iodine was applied to site of injection. Using a 30-gauge needle, 0.05 ml ranibizumab was injected through temporal clear cornea injection with the head of needle within the limits of the center of the iris. Postoperatively, a topical antibiotic (ofloxacin) was administered four times daily for 7 days.

RESULTS

The patients were followed every month. Both initial ophthalmic examination and each follow-up included: evaluation of best-corrected distant VA using an EDTRS chart, slit-lamp examination, a fundus exam with dilated pupils, specular microscopy, FA, evaluation of retinal architecture and measurement of foveal thickness using the OCT, evaluation of worsening of subjective metamorphopsia. Any ocular or systemic adverse events were also recorded.
There were four (40%) male and six (60%) female patients. The mean axial length was 27,6 mm (range, 25.7-31.3 mm). The mean initial VA was 0.19 (decimal equivalent), with a range from 0.06 to 0.5. A statistically significant improvement to a mean VA of 0.33 decimal equivalent (log-MAR:0.48) was demonstrated at the final follow-up.
The patient presented asymptomatically without eye pain, redness, tearing or photophobia during our follow-up.
On slit-lamp examination, there was no anterior chamber cell or flare and vitreous examination revealed no cell. There was not ciliary injection, small keratic precipitates, anterior chamber cell or flare. Vitreous cell was not detected.
Corneal endothelial cell counts were done using a non-contact specular microscope: there wasn't a significant decrease in postoperative endothelial cell densities when compared to preoperative values. Mean preoperative endothelial cell densities were 2035 +/-270 cells/mm2; mean endothelial cell densities were 2022 +/-281 cells/mm2 at the final follow-up; the difference was not statistically significant.
All patients had retinal abnormalities consistent with pathologic myopia: all eyes were aphakic and had myopic retinal abnormalities such as peripheral retinal degeneration or retinal tears (treated by argon laser).Two case showed previous retinal detachment in the fellow eye.
The number of intravitreal injections administered for each patient was 3. None additional monthly injections was performed in eyes because we had not patients with persistent CNV leakage after 3 months: all eyes had angiographic closure after 3 monthly trans-corneal injections of ranibizumab.
The OCT results also showed significant reduction in CMT after treatment. Mean central macular thickness (CMT) measured with OCT was 340 µm (range, 179-663 µm) at the baseline, and was reduced significantly at the final follow-up to 212µm (range, 125-455 µm).
It is interesting to notice that none patient had worsening of subjective metamorphopsia.
One potential risk that should be considered in the treatment of myopic CNVs with anti-VEGF is the possible formation of marginal crack lines after treatment-related contraction of the myopic CNVs, which was considered an indication of early damage of retinal pigment epithelium that might lead to expanding macular chorioretinal atrophy [19]. No marginal crack lines were noted during our follow-up.
No ocular or systemic complications were noted after our injections (Table 1).

Table I. Pars plana injection Vs our trans-corneal injection: number of complications.

Adverse event/ Complication	*Intravitreal administration via pars plana Studies: FVF2598g(MARINA) FVF2587g(ANCHOR) FVF3192(PIER)*	*Administration by anterior chamber (our method)*
IOP increased	15.7%(ANCHOR)-16.3%(MARINA)	10%
Retinal detachment	0.4%(MARINA)-1.4%(ANCHOR)	0%
Retinal haemorrhage	16.7%(MARINA)-18.6%(ANCHOR)	0%
Subretinal fibrosis	4.2%(MARINA)-12.9%(ANCHOR)	0%
Uveitis	0.4%(MARINA)-0.7%(ANCHOR)	0%
Vitritis	5.5%(MARINA)-8.6%(ANCHOR)	0%
Endophthalmitis	0%(PIER)-0.4%(MARINA)-0.7%(ANCHOR)	0%
Retinal artery occlusion	0%(MARINA-ANCHOR)	0%
Retinal tear	0%(ANCHOR)-0.4%(MARINA)	0%

DISCUSSION

No generally accepted and satisfactory treatment protocol exists for patients with CNV secondary to PM. In former years, before anti-VEGF drugs became available, PDT was considered as the only treatment option. Angiogenesis is regulated by several proangiogenic and antiangiogenic factors, many of which have now been identified. VEGF has been found to be one of the key elements in angiogenesis. Tong et al [20] showed that the VEGF concentrations in aqueous humour were markedly increased in patients with CNV secondary to PM when compared with the controls. Several studies demonstrated promising short term results for the treatment of CNV in PM with off-label use of the intravitreal anti-VEGF drug bevacizumab [21,22,23,24,25].

Recently, several authors reported the benefit of intravitreal ranibizumab for myopic CNV[8,9,10].

The primary objective for our study was to evaluate the efficacy of ranibizumab by anterior chamber injections in preventing vision loss and to evaluate the safety and tolerability of our trans-corneal injections of ranibizumab (administered monthly). We prove the same efficacy of trans-corneal ranibizumab vs. intravitreal ranibizumab administration: the 6-month outcomes suggest trans-corneal ranibizumab to be a promising treatment method for CNV secondary to PM in aphakic patients, resulting in both visual and anatomic improvements, without any complications (TABLE 1). It is interesting to notice that we did not observe peripheral retinal break and/or retinal detachment after trans-corneal injection in our predisposed hypermyopic patients: retinal detachment is more frequent in hypermyopic patients with peripheral retinal degeneration.

One patient had intra-ocular pressure (IOP) rise, but the elevated IOP was manageable, easily monitored and not serious. Therefore, this adverse event is clearly outweighed by the superior efficacy of the study drug.

In conclusion we show that in this small series of eyes with limited follow-up ranibizumab by anterior chamber administration seems to be a safe and effective treatment for CNV secondary to pathologic myopia.

Further studies to evaluate the safety, efficacy and optimal treatment regimen are justified.

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