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RETINAL DISORDERS

OLIMPIC: a 12-month study on the criteria driving retreatment with ranibizumab in patients with visual impairment due to myopic choroidal neovascularization

Federico Ricci[1] · Giovanni Staurenghi[2] · Monica Varano[3] · Chiara Eandi[4] · Tommaso Lupieri Sinibaldi[5] · Laura Colombo[5] · Marta Bartezaghi[5] · Stefania Bassanini[5]

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Abstract

Purpose To evaluate criteria driving retreatment with ranibizumab in Italian patients with myopic choroidal neovascularization (mCNV).

Methods OLIMPIC was a 12-month, phase IIIb, open-label study. Patients with active mCNV were treated with ranibizumab 0.5 mg according to the European label. The study assessed local criteria in Italy driving retreatment decisions with ranibizumab; and the efficacy, safety, and tolerability of ranibizumab.

Results The mean (standard deviation [SD]) age of treated patients ($N = 200$) was 61.8 (12.7) years; range 22–85 years. The multivariate regression model indicated that presence of active leakage (odds ratio [OR] 95% confidence interval [CI]: 11.30 [1.03–124.14]), presence of intraretinal fluid (OR [95%CI]: 28.21 [1.55–513.73]), and an improvement in best-corrected visual acuity (BCVA) from baseline < 10 letters (OR [95%CI]: 17.60 [1.39–222.75]) were the factors with the greatest effect on retreatment with ranibizumab. The mean (SD) BCVA gain from baseline to month 12 was 8.4 (12.8) letters ($P < 0.0001$). The mean (SD) number of injections was 2.41 (1.53); range 1–9. Ocular and non-ocular adverse events were reported in 41 (20.5%) and 30 (15.0%) patients, respectively.

Conclusions Individualized treatment with ranibizumab was effective in improving BCVA in patients with mCNV over 12 months. Both anatomical and functional variables had significant effects on causing retreatment. There were no new safety findings.

Trial registration www.ClinicalTrials.Gov (NCT No: NCT02034006)

Keywords Choroidal neovascularization · Pathologic myopia · Ranibizumab · Retreatment criteria · Visual acuity · Visual impairment

Meeting presentations: Data from the study were presented at the FLORETINA congress: Florence April 27–30, 2017.

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✉ Federico Ricci
rccfrc00@gmail.com

[1] Retina Diseases Unit, Referral Center for Diagnosis and Therapy of AMD and Sight Threatening Retinal Diseases, PTV Foundation/Tor Vergata University, Viale Oxford, 81, 00133 Rome, Italy

[2] Department of Biomedical and Clinical Science Luigi Sacco, Luigi Sacco Hospital, University of Milan, Milan, Italy

[3] IRCCS–Fondazione Bietti, Rome, Italy

[4] Department of Surgical Sciences, Eye Clinic, University of Torino, Via Juvarra 19, 10122 Turin, Italy

[5] Novartis Farma SpA, Largo Umberto Boccioni 1, 21040 Origgio, VA, Italy

Introduction

Pathologic myopia (PM)—also known as high, degenerative, or malignant myopia [1]—is characterized by a refractive error of ≥ − 6 Diopter (D); axial length ≥ 26 mm; and degenerative changes involving the sclera, choroid, and retina [2, 3]. PM affects mainly the younger population (age < 50 years) [4–6], and is associated with a reduction in the quality of life (QoL) of the affected patients and is a socio-economic burden on society [7, 8]. Approximately 5–10% patients with PM develop myopic choroidal neovascularization (mCNV) [8], which is the most common vision-threatening complication of PM. The long-term prognosis of mCNV is poor if left untreated [5, 9–11].

Vascular endothelial growth factor (VEGF) is thought to have an important role in the pathogenesis of mCNV as it triggers angiogenesis and its levels are increased in eyes with mCNV [12–14]. Ranibizumab was the first anti-VEGF agent to be approved for the treatment of visual impairment secondary to mCNV based on the results from the RADIANCE [15] and REPAIR [16, 17] studies, which demonstrated superior visual and anatomical outcomes with ranibizumab. Following an initial injection, the current label of ranibizumab 0.5 mg for mCNV recommends monthly monitoring, and retreatment is determined by the physician based on disease activity, as assessed by visual acuity (VA) and/or anatomical parameters [18].

The OLIMPIC study (NCT02034006) [19] was designed to assess local criteria in Italy driving retreatment decisions with ranibizumab and to evaluate efficacy, safety, and tolerability of ranibizumab in Italian patients diagnosed with visual impairment due to mCNV.

Methods

Study design

OLIMPIC was a prospective, 12-month, phase IIIb, open-label, interventional, multicenter study in patients with visual impairment due to mCNV. The study was conducted from June 2014 to July 2016 across 33 centers in Italy (see Table, Online resource 1, which shows the list of study centers) and did not impose a fixed monthly visit scheme, used for registrative trial. The design used is very close to clinical practice.

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol (and all its amendments) was reviewed by the Independent Ethics Committee for each center. Patients provided written informed consent before entering the study.

Patients

Participants ≥ 18 years of age were included if they were diagnosed with active mCNV (as confirmed by the presence of high myopia with > − 6 D of spherical equivalence, posterior changes compatible with PM detected by fundus ophthalmoscopy and fundus photography, active leakage from CNV observed through fluorescein angiography (FA), and intra/subretinal fluid (IRF/SRF) observed using optical coherence tomography (OCT)) and had a best-corrected visual acuity (BCVA) > 24 and < 78 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent of approximately 20/32 to 20/320).

If both eyes were eligible, the eye with the worse VA at baseline was selected for treatment, except when medical reasons or local ethical requirements required selection of the eye with better VA.

Patients were excluded if they had an active infectious disease or intraocular inflammation in either eye at the time of enrolment; ocular disorders in the study eye requiring medical or surgical intervention or resulting in compromised VA; received pan-retinal or focal/grid laser photocoagulation with involvement of the macular area in the study eye at any time; or received intraocular treatment with any anti-VEGF, verteporfin photodynamic therapy, or any intraocular surgery or corticosteroid administration within 1 month before study entry; uncontrolled blood pressure; or a history of stroke or other medical conditions that could have influenced the study outcome. Women of childbearing potential not using effective methods of contraception, and pregnant or nursing women were also excluded.

Treatment

All eligible patients received a single initial intravitreal injection of ranibizumab 0.5 mg as per the approved label [18]. Mandatory monitoring visits were planned monthly for the first 3 months, and then at the 6 and 12 month after the first administration of ranibizumab, with a tolerance of 7 days. Optional visits could be possible outside of the pre-planned visits, but were not tracked in the electronic case record form. Further injections were administered if monitoring indicated the presence of disease activity, based on functional and/or anatomical features as per local clinical practice and as per approved label.

Objectives

The primary objective was to investigate the current criteria driving retreatment in Italian patients affected by mCNV and experiencing a relapse of the disease after the first administration of ranibizumab. Both anatomical (signs of lesion activity evaluated through clinical examination and/

or OCT, and/or FA) and/or functional (reduction in BCVA) criteria were considered during the analysis.

The secondary objectives included evaluation of the mean change in BCVA at months 6 and 12 compared with baseline; the number of ranibizumab injections administered over the 12-month study period; time to relapse/retreatment; and safety and tolerability.

Assessments

Efficacy

Both functional and anatomical parameters were assessed locally by investigators or trained technicians at each site. Efficacy assessments were conducted before administration of ranibizumab on the day of treatment.

BCVA: BCVA was tested at each visit until month 12 using the ETDRS charts. BCVA measurements were taken in a sitting position at an initial test distance of 4 m using ETDRS charts. Refractive error was expressed in D.

OCT: Central subfield thickness (CSFT); central subfield volume (CSV); and presence of macular edema, IRF, cysts, and SRF were assessed using OCT at screening and months 2, 6, and 12.

FA: Evidence of CNV and presence of active leakage were assessed on FA at screening and months 2 and 6.

Clinically significant abnormalities assessed at fundus ophthalmoscopy and as per physician's opinion (hemorrhage, pigment clumping, retinal pigment epithelium atrophy).

Safety

All adverse events (AEs) and serious adverse events (SAEs) were assessed over the entire 12-month study duration.

Statistical analysis

The planned sample size was 200 patients; assuming around 70% of patients would need retreatment, this meant that the primary endpoint could be evaluated in approximately 140 patients.

For the primary endpoint, a multivariate regression model was fitted considering the following covariates, using a stepwise procedure: presence of IRF (yes/no); presence of macular edema (yes/no); presence of cysts (yes/no); presence of active leakage (yes/no); presence of SRF (yes/no); clinically significant abnormalities, defined as any abnormal signal at the fundus examination, performed at each time point, assessed by means of a slit lamp and indirect stereo ophthalmoscope, as per clinical judgment (yes/no); change in macular volume versus previous visit; change in central retinal thickness versus previous visit; an improvement in BCVA < 5 letters (yes/no); an improvement in BCVA < 10 letters (yes/no); and change from baseline in BCVA classified as worsened (loss of ≥ 5 letters), stable (loss of ≥ 4 letters to gain of ≤ 4 letters), or improved (gain of ≥ 5 letters). A significance level of 0.3 was required to allow a variable into the model, and a significance level of 0.35 was required for a variable to remain in the model. Moreover, a univariate logistic regression model was applied to each of the aforementioned covariates.

A sensitivity analysis was then performed at month 2, which considered a patient as retreated if their first retreatment took place < 30 days after the month 2 assessment, in order to better evaluate the effect of each covariate. For all analyses, the independent variables were considered at the closest timepoint to the first retreatment. In case a value was not recorded at the scheduled assessment, the value was considered missing.

A Wilcoxon signed rank test was used to analyze changes in BCVA. A Wilcoxon/Mann-Whitney *U* test was used in case of non-normally distributed data for comparison of naïve versus treated patients. OCT and FA parameters were summarized using descriptive statistics. Time to retreatment in days was presented overall by Kaplan-Meier estimates and summarized by median, 25th and 75th percentiles, and their 95% confidence interval (CI). Efficacy was analyzed in the full analysis set (FAS) which included all patients who received at least one dose of ranibizumab.

Safety was analyzed in the safety analysis set which included all patients who received at least one dose of ranibizumab and had at least one post-baseline safety assessment. The safety results were summarized.

All analyses were carried out using SAS® for Windows release 9.4 (64-bit) or later (SAS Institute Inc., Cary, NC, USA).

Results

Of the 215 patients screened, 200 patients underwent a baseline visit and received one injection of ranibizumab 0.5 mg. All 200 patients were included in the FAS and safety set. Fourteen (7%) patients discontinued the study before the 12-month study visit. The reasons for discontinuation were consent withdrawn ($n = 7$), lost to follow-up ($n = 5$), death ($n = 1$), and pregnancy ($n = 1$, Fig. 1).

The mean (± standard deviation [SD]) age of the patients was 61.8 (12.7) years (range 22–85 years), 73.5% were female, and 99.5% patients were Caucasian. Bilateral PM was present in 79.5% patients and bilateral CNV in 13% patients. The most common CNV subtype observed was subfoveal CNV (61.0% patients). Median time from CNV diagnosis to informed consent was 0.89 (Interquartile range 0.10–14.74 months) (Table 1).

Of the 200 patients, 147 (73.5%) were anti-VEGF treatment-naïve at baseline. During the study, 70 (35%) patients were treated with ranibizumab 0.5 mg only once (defined as

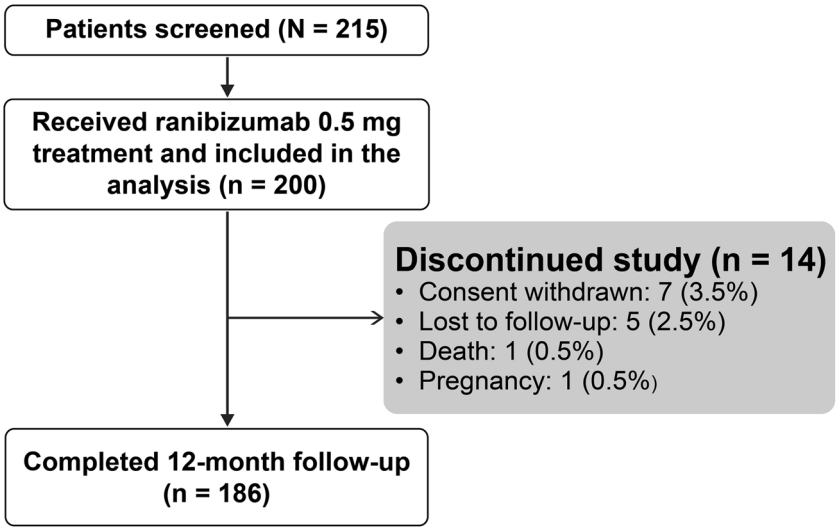

Fig. 1 Patient disposition

treated patients), and 130 (65%) patients were treated with ranibizumab more than once (defined as retreated patients). There were no differences in baseline characteristics between the treated and retreated cohorts or between the prior anti-VEGF treated and treatment-naïve cohorts (Table 1).

Efficacy

The multivariate regression model indicated presence of active leakage (OR [95%CI]: 11.30 [1.03–124.14]), presence of IRF (OR [95%CI]: 28.21 [1.55–513.73]), and an improvement in BCVA from baseline < 10 letters (OR [95%CI]: 17.60 [1.39–222.75]) to be the factors with the greatest effect on retreatment. The univariate model analysis indicated macular edema ($P < 0.0001$), presence of active leakage ($P < 0.0001$), presence of cysts ($P < 0.0001$), presence of IRF ($P < 0.0001$), presence of clinically significant abnormalities ($P = 0.0103$), and an improvement in BCVA of < 10 letters from baseline ($P = 0.0114$) to be the factors with a statistically significant association to retreatment (Fig. 2).

The sensitivity analysis at month 2 based on the multivariate regression model confirmed the presence of IRF and active leakage at month 2 to be the factors most likely to drive retreatment. The univariate model showed the presence of active leakage, IRF, SRF, cysts, and macular edema to be the factors strongly associated with retreatment.

BCVA outcomes

There was a notable gain in mean (SD) BCVA from baseline (54.66 [16.86]) to month 6 and to month 12 (7.51 [11.68] and 8.42 [12.81] ETDRS letters, respectively, both $P < 0.0001$, Fig. 3). The mean (SD) BCVA at baseline in patients who were anti-VEGF treatment-naïve or anti-VEGF-treated was 54.93 (17.00) and 53.89 (16.61) letters, respectively. The gain from baseline to month 12 or time of premature discontinuation was similar in patients who were prior anti-VEGF treatment-naïve or anti-VEGF-treated (8.32 [13.41] and 8.69 [11.12] ETDRS letters, respectively, both $P < 0.0001$, Fig. 3).

At month 12 or premature discontinuation, the proportion of patients gaining ≥ 5 and ≥ 10 ETDRS letters in the treated/retreated cohorts was 84.3/75.0% and 54.9/52.2%, respectively.

The mean (SD) refractive error remained stable in the study eye over the study duration, − 7.25 (6.09) D at baseline versus − 7.28 (6.51) D at month 12 or premature study discontinuation.

Anatomical outcomes

The foveal thickness decreased over time, and the mean (SD) change in CSFT from baseline (361.57 [92.16] μm) to months 6 and 12 or premature discontinuation was − 41.45 (77.88) and − 35.72 (95.28) μm, respectively (both $P < 0.0001$; Fig. 4). The mean (SD) CSFT at baseline was 335.98 (97.64) μm in the treated cohort and 374.97 (86.56) μm in the retreated cohort. The mean change in CSFT from baseline to month 12 was higher in retreated patients compared with treated patients (Fig. 4).The mean (SD) change in CSV from baseline (0.28 [0.07] mm^3) at months 6 and 12 was − 0.02 (0.07) mm^3 and − 0.02 (0.09) mm^3, respectively (both $P < 0.0001$). The mean (SD) CSV at baseline was 0.27 (0.08) mm^3 in the treated cohort and 0.29 (0.07) mm^3 in the retreated cohort; the reduction in CSV at month 12 was similar in treated and retreated patients (− 0.02 [0.07] mm^3 and − 0.01 [0.10] mm^3, respectively).

The proportion of patients with macular edema, SRF, IRF, and cysts decreased from baseline to month 12 or premature discontinuation (see Fig, Online resource 2, which shows the proportion of patients with macular edema, SRF, IRF, and

Table 1 Baseline demographics and disease characteristics (full analysis set)

Characteristics	Total (N = 200)	Treated patients[a] (n = 70)	Retreated patients[a] (n = 130)	Prior anti-VEGF treated (n = 53)	Prior anti-VEGF treatment-naïve (n = 147)
Mean (SD) age, years	61.8 (12.7)	61.3 (13.0)	62.1 (12.5)	61.3 (12.4)	62.0 (12.8)
Gender, n (%)					
Female	147 (73.5)	53 (75.7)	94 (72.3)	39 (73.6)	108 (73.5)
Race, n (%)					
Caucasian	199 (99.5)	69 (98.6)	130 (100.0)	53 (100.0)	146 (99.3)
Type of CNV, n (%)					
Subfoveal	122 (61.0)	37 (52.9)	85 (65.4)	39 (71.7)	84 (57.1)
Juxtafoveal	61 (30.5)	25 (35.7)	36 (27.7)	11 (20.8)	50 (34.0)
Extrafoveal	17 (8.5)	8 (11.4)	9 (6.9)	4 (7.6)	13 (8.8)
Median (IQR) time between diagnosis of CNV secondary to PM and signing informed consent, months	0.89 (0.10–4.74)	0.89 (0.07–4.72)	0.85 (0.16–14.78)	15.80 (9.10–56.05)	0.36 (0.03–1.71)
Mean (SD) VA	54.66 (16.86)	–	–	53.89 (16.61)	54.93 (17.00)

CNV, choroidal neovascularization; *IQR*, interquartile range; *PM*, pathologic myopia; *SD*, standard deviation; *VA*, visual acuity; *VEGF*, vascular endothelial growth factor

[a] During the study

cysts during the study). The reduction in these anatomical parameters was more prominent in treated patients compared with retreated patients (see Fig, Online resource 2).

FA characteristics

At baseline, most patients underwent FA (187/200, 93.5%), and all, except 1 (1.56%) patient in treated cohort, had evidence of active CNV; this proportion decreased at month 2 (n = 121/180; 67.2%) and month 6 (n = 118/175; 67.4%) after ranibizumab treatment. The reduction from baseline at months 2 and 6 was observed in both treated and retreated cohorts.

At baseline, 182 of 187 patients undergoing FA (97.3%) showed active leakage. This proportion decreased at month 2 (n = 59/180; 32.8%) and month 6 (n = 44/175; 25.1%) after ranibizumab treatment (see Fig, Online resource 3, which shows the proportion of patients with active leakage from baseline to month 6).The reduction was observed in both treated and retreated cohorts at months 2 and 6 (see Fig, Online resource 3).

Treatment exposure

The mean (SD) number of injections in the FAS was 2.41 (1.53); range 1–9, the mean (SD) number of injections per retreated patient was 3.17 (1.40). Overall, 26.5%, 19.5%, and 8.5% of patients received two, three, or four injections, respectively, prior to month 12. Kaplan-Meier analysis of time to first retreatment showed that the median time for a patient to be free from retreatment was 3.15 months (95%CI: 2.33, 5.09 months, Fig. 5). This median time to relapse was similar in those who were anti-VEGF treatment-naïve or anti-VEGF-treated at baseline (3.19 and 3.15 months, respectively, Fig. 5).

Safety

Overall, at least one ocular or non-ocular AE was reported in 41 (20.5%) and 30 (15.0%) patients, respectively. Ocular SAEs were reported in two patients and non-ocular SAEs were reported in five patients (Table 2). Two AEs were suspected to be related to ranibizumab; both were ocular events (see Table, Online resource 4, which lists the drug-related AEs).

Two AEs, both non-ocular events (maternal exposure during delivery and spontaneous abortion) that occurred in one and the same patient, resulted in study discontinuation. Both events were suspected to be not related to ranibizumab. There were no cases of endophthalmitis. One death was reported during the study (due to cardiac arrest) and was considered by the investigator to be not related to treatment.

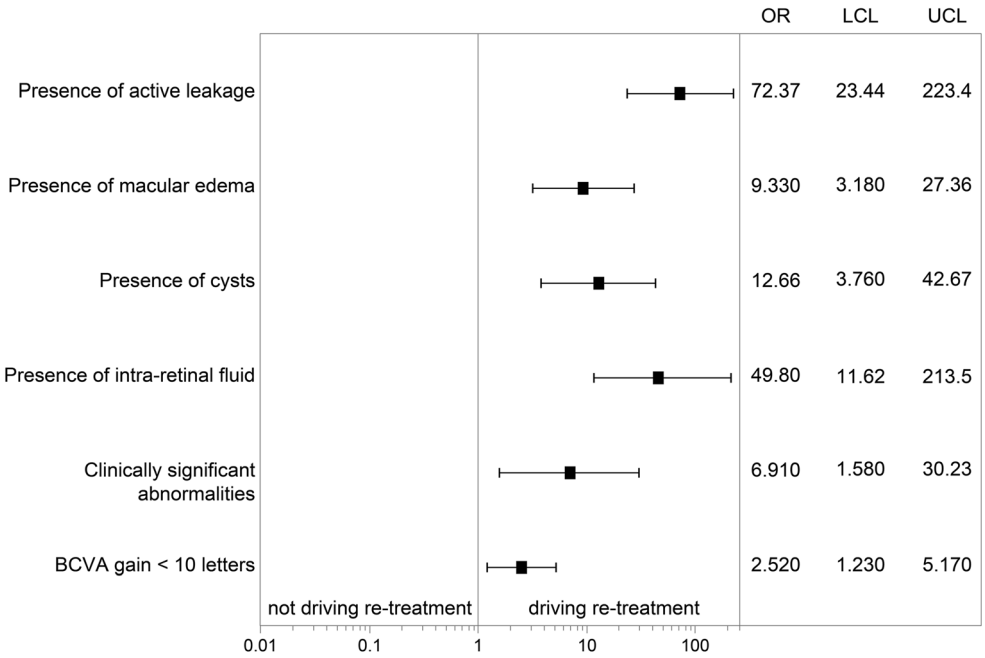

Fig. 2 Criteria driving retreatment (full analysis set). Univariate logistic regression model. BCVA, best-corrected visual acuity; LCL, lower confidence limit; OR, odds ratio; UCL, upper confidence limit

Discussion

The current European label for ranibizumab recommends individualized treatment based on disease activity, as assessed by VA and/or anatomical parameters, for patients with visual impairment due to mCNV [18]. In the OLIMPIC study, the results of the multivariate analysis showed two anatomical parameters (active leakage and IRF) and one VA parameter (improvement in BCVA from baseline < 10 letters) to be the factors most likely to drive retreatment. This finding was confirmed by the univariate model analysis results; of the 6 factors shown to drive retreatment, five were anatomical and the sixth was an improvement in BCVA from baseline < 10 letters. The sensitivity analyses performed at month 2 (both univariate and multivariate regression models) also showed anatomical parameters to be the main criteria driving retreatment.

The baseline characteristics of patients in this study were generally consistent with those reported previously in mCNV patients [15, 16, 20–22], in that most patients were female and

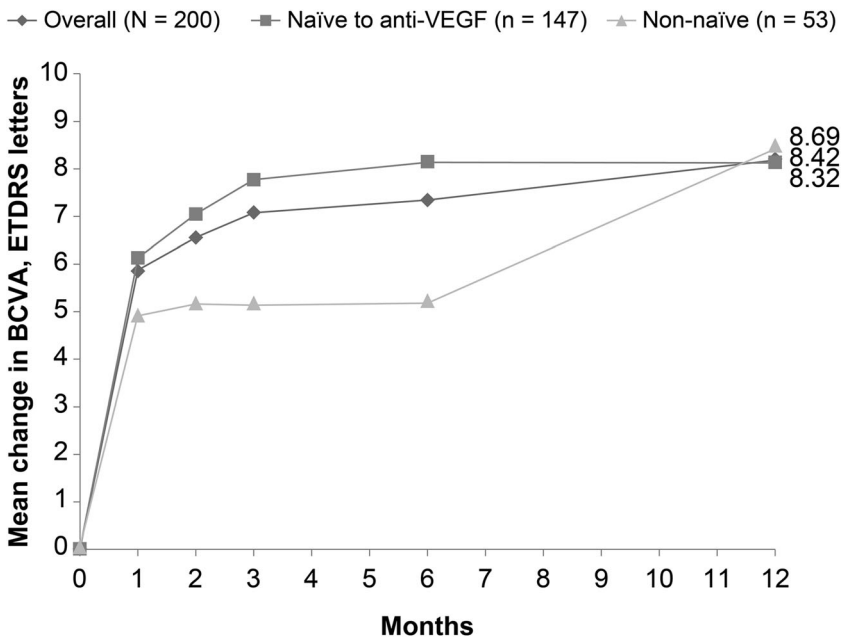

Fig. 3 BCVA gain from baseline to month 12 or premature discontinuation (full analysis set). BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor

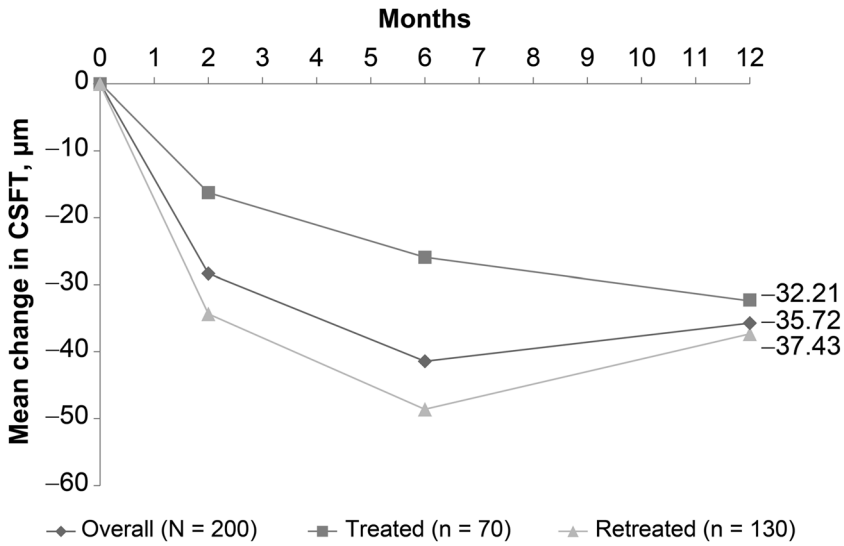

Fig. 4 CSFT reduction from baseline to month 12 or premature discontinuation (full analysis set) CSFT, central subfoveal thickness

the location of CNV was subfoveal in the majority of patients. However, patients in this study were older than those in the RADIANCE study (mean age ~ 62 years in OLIMPIC vs ~ 56 years in RADIANCE [15]). Ranibizumab treatment resulted in notable BCVA improvements at month 12 (+ 8.42 letters), which corroborated the benefits observed with ranibizumab in the RADIANCE and REPAIR studies (+ 14.4 letters and + 13.8 letters, respectively) [15, 17]. The nearly 1-line lower VA gain in OLIMPIC than that observed in RADIANCE could be related to the fact that patients enrolled in the OLIMPIC study were older, and a higher proportion had non-subfoveal lesions (61% in OLIMPIC vs ~ 70% in RADIANCE); also both treated and treatment-naïve patients were included. The VA improvements with ranibizumab have been shown to be maintained over the long term for up to 4 years in mCNV patients [23–26].

In patients with mCNV, it has been observed that VA improvements with ranibizumab occur irrespective of whether patients are treatment-naïve at baseline or not [27], whereas in other indications, better VA outcomes with ranibizumab treatment have been observed in treatment-naïve patients, which could be related to the difference in

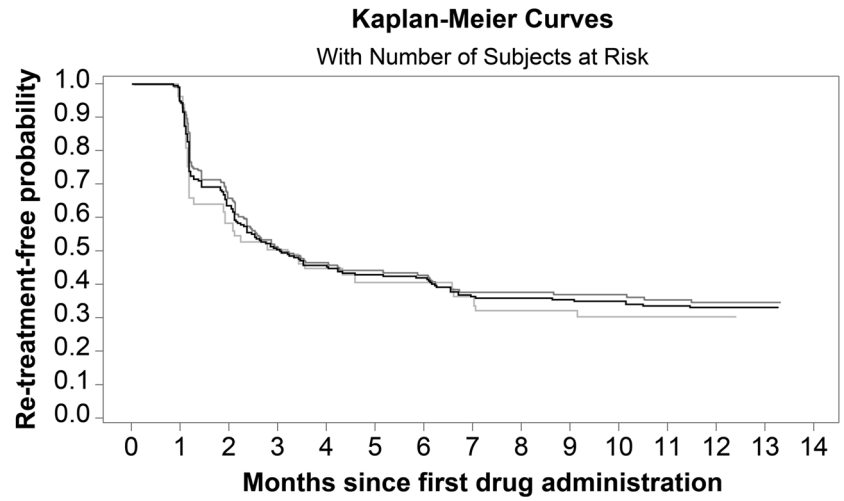

Fig. 5 Time to first retreatment (full analysis set) Kaplan-Meier curves showing number of patients at risk. CI, confidence interval; VEGF, vascular endothelial growth factor

Subjects	Mean time (months)	Median time (months)	95%CI (lower limit, upper limit)
Overall	5.57	3.15	(2.33, 5.09)
Naïve to anti-VEGF	5.62	2.96	(2.33, 6.01)
Non-naïve	4.67	3.38	(1.87, 6.90)

Table 2 Key ocular and non-ocular AEs and SAEs (safety set)

Preferred term, *n* (%)*	Ranibizumab 0.5 mg (*N* = 200)
Ocular AEs, total†	41 (20.5)
CNV	7 (3.5)
Conjunctival hemorrhage	4 (2.0)
Conjunctival hyperemia	2 (1.0)
Metamorphopsia	2 (1.0)
Retinal hemorrhage	2 (1.0)
VA reduced	2 (1.0)
Expired product administered	2 (1.0)
Non-ocular AEs, total†	30 (15.0)
Influenza	7 (3.5)
Headache	2 (1.0)
Hypertension	2 (1.0)
C-reactive protein abnormal	2 (1.0)
Ocular SAEs, total	2 (1.0)
Expired product administered$	2 (1.0)
Non-ocular SAEs, total	5 (2.5)
Atrioventricular block	1 (0.5)
Cardiac arrest	1 (0.5)
Cholecystitis acute	1 (0.5)
Klebsiella sepsis	1 (0.5)
Spontaneous abortion	1 (0.5)
Ovarian cyst	1 (0.5)

Terms were coded using Medical Dictionary for Regulatory Activities dictionary, version 18.1.

AE, adverse event; *CNV*, choroidal neovascularization; *SAE*, serious adverse event; *VA*, visual acuity

*Each patient could experience more than one AE/SAE. Patients were counted only once in each row

† Patients with at least one event

$ One patient received the expired study medication by mistake nearly 11 months after starting study medication. The patient reported no systemic or local AE's as a consequence of the injection and recovered on the same day. No action was taken with regard to study medication due to the event. The other patient received the expired study medication by mistake 5 months and few days after starting study medication. No treatment was administered due to the event and no action was taken with regard to study medication. The patient completely recovered from the event on the same day

etiology of mCNV. Similarly, in the OLIMPIC study, there were no notable between-group differences, although the BCVA gain was numerically higher in anti-VEGF treatment-naïve patients.

In elderly patients, the inability to differentiate if CNV is related to pathologic myopia or to age-related macular degeneration is a known bias. In the pivotal phase 3 trials of ranibizumab and aflibercept in mCNV [15, 28], there were no upper limit in age for patient recruitment. In both the phase 3 studies, as well as the OLIMPIC study, all patients' ≥ 18 years of age were eligible if affected with pathologic myopia and CNV. The mean (SD) age at baseline in the OLIMPIC study was 61.8 (12.7) years, range 22–85 years; in the ranibizumab groups in RADIANCE study was 54.0 (14.0) years, range 18–87 years (data on file) in group I and 56.1 (14.4) years, range 19–85 years (data on file) in group II; and in the aflibercept group in MYRROR study was 58.5 (13.17) years, range 23–87 years. As the inclusion criteria in the OLIMPIC study was similar to that in RADIANCE [15] and MYRROR [28], it has more or less the same bias with relation to age as that observed in the phase 3, registration studies that led to approval of ranibizumab and aflibercept for mCNV.

The anatomical outcomes corroborated with the BCVA improvements: there was a rapid reduction in CSFT at month 3 that gradually reduced further up to month 12. The change in CSFT was more prominent in retreated patients. The proportion of patients with macular edema, SRF, IRF, cysts, and active leakage also decreased over time. FA is considered the current standard of care for evaluating mCNV activity [23, 29, 30]. Most patients (93.5%) underwent FA analysis at screening in our study and all except one patient had evidence of mCNV. Ranibizumab treatment was associated with a reduction in the proportion of patients with active CNV and active leakage over time. In mCNV, the decision regarding retreatment needs a comprehensive approach to the disease. Although perception of metamorphopsia, VA changes, fundus examination, and OCT are often sufficient to indicate the need for retreatment, FA is an important tool to guide retreatment decisions for active mCNV [23, 29, 30].

Previous studies in patients with mCNV have shown that, on average, patients may require one to four anti-VEGF injections during the first year of treatment [15, 17, 27, 31–33]. Consistent with these reports, in our study, the mean number of ranibizumab injections was 2.41 over 12 months. After the mandatory first injection, 35% of patients did not require another injection, and 46% of patients required only one or two additional injections over the 12-month duration. The median treatment-free interval was 3.15 months, indicating that patients with mCNV may need less frequent monitoring compared with other ocular disorders.

The safety findings were consistent with the safety results from the pivotal trials and the known safety profile of ranibizumab [15–18]. The incidence of serious ocular and non-ocular AEs was low. There were no cases of endophthalmitis.

The limitations of the study are its open-label nature and lack of a placebo control. Furthermore, the study did not include classification of the staphyloma subtype. Although functional and anatomical outcomes were assessed in the study according to protocol, OCT and FA were not performed at each study visit, and FA was not assessed at the 12-month visit. Moreover, no central reading center was involved in the assessment of OCT and FA outcomes: despite procedures being described in the study protocol, a certain amount of

variability in the assessment could be possible, in particular regarding potential overlapping criteria such as IRF, macular edema or intraretinal cysts, impacting the final anatomical outcomes and evaluation of the primary endpoint.

In conclusion, the OLIMPIC study confirmed that individualized treatment with ranibizumab is effective in improving and sustaining BCVA in patients with myopic CNV over 12 months. Many patients may only need one or two injections during the first year. Based on disease activity, the need for retreatment can be assessed by VA and/or anatomical parameters, but the latter were found to be the factors most likely to drive retreatment in this study.

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Compliance with ethical standards

Conflict of interest Federico Ricci received consultation fees and travel grants from Alcon, Allergan, Bayer, Novartis and SIFI. Giovanni Staurenghi is a consultant/advisor for Heidelberg Engineering, Quantel Medical, Carl Zeiss Meditec, Alcon, Allergan, Bayer, Boehringer Ingelheim, Genentech, GSK, Novartis, Roche; has received grant support from Heidelberg Engineering, Optos, Optovue, Quantel Medical, Centervue; has received lecture fee from Alcon, Allergan, Bayer, GSK, Novartis, Roche; and patents/royalty from Ocular Instruments. Monica Varano received sponsorship from Allergan, Bayer, Novartis, and SIFI. Chiara Eandi received consultation fees and travel grants from Allergan, Bayer, Novartis, Optovue, and Thea. Marta Bartezaghi and Stefania Bassanini are employees of Novartis Farma SpA, Italy. Laura Colombo and Tommaso Lupieri Sinibaldi were employees of Novartis Farma SpA, Italy at the time of the study. This study was funded by Novartis Farma SpA, Italy.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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