TREATMENT OF EXUDATIVE AGE-RELATED MACULAR DEGENERATION WITH RANIBIZUMAB COMBINED WITH KETOROLAC EYEDROPS OR PHOTODYNAMIC THERAPY

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Purpose: To evaluate whether ketorolac eyedrops plus intravitreal ranibizumab (IVR) or verteporfin photodynamic therapy plus IVR provides additional benefit over IVR monotherapy for treatment of choroidal neovascularization in age-related macular degeneration.

Methods: This was a prospective, randomized, pilot study in 75 patients with naive choroidal neovascularization. Patients were randomized 1:1:1 into 3 groups: ranibizumab monotherapy (RM), ranibizumab plus ketorolac, or ranibizumab plus loading-phase reduced-fluence verteporfin photodynamic therapy (RV) groups.

Results: At 12 months, all groups showed significant improvement in both best-corrected visual acuity and central retinal thickness. The mean best-corrected visual acuity change from baseline to 12 months was $-0.14 \pm 0.52$ logMAR, $-0.25 \pm 0.60$ logMAR, and $-0.10 \pm 0.30$ logMAR in RM, ranibizumab plus ketorolac, and RV groups, respectively. The mean central retinal thickness change from baseline to 12 months was $-125 \pm 15\, \mu m$, $-141 \pm 21\, \mu m$, and $-130 \pm 15\, \mu m$ in RM, ranibizumab plus ketorolac, and RV groups, respectively. Both ranibizumab plus ketorolac and RV groups required fewer IVR treatments than RM.

Conclusion: Compared with RM and ranibizumab plus verteporfin photodynamic therapy, the combination of 0.45% ketorolac eyedrops 3 times a day and ranibizumab in patients with choroidal neovascularization provided superior best-corrected visual acuity and central retinal thickness outcomes. Both combination regimens required fewer IVR injections than RM during the 12-month follow-up period.

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In developed countries, age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness in patients older than 60 years. Typical features of neovascular AMD include choroidal neovascularization (CNV) underneath the fovea, which is associated with choroidal hemorrhage and retinal swelling.

Vascular endothelial growth factor (VEGF) plays a major role in the development of CNV in AMD. Monthly injections of intravitreal ranibizumab (IVR), the Fab fragment of a recombinant humanized monoclonal antibody that inhibits all isoforms of VEGF, decrease the possibility of vision loss, and improve visual acuity in patients with CNV in AMD. However, because of the burden associated with monthly intravitreal injections, alternative regimens including as-needed (pro re nata) treatment have been investigated, with outcomes almost equivalent to those of the Phase III clinical studies.
It is important to note that VEGF is not the only causative factor in CNV. Free radicals and oxidized lipoproteins in the aging retina are major local triggers of parainflammation, which is the chronic status responsible for the initiation and progression of age-related chorio-retinal damage.7 Thus, inflammation also plays an important role in the development of CNV, and administration of a topical non-steroidal anti-inflammatory drug (NSAID) has been shown to supplement the activity of IVR in reducing the central retinal thickness (CRT)8-10 and the rate of re-injection in CNV.11

Randomized comparisons of different NSAIDs have shown that 0.45% ketorolac achieved significantly higher aqueous concentrations and prostaglandin E2 inhibition than 0.09% bromfenac and 0.1% nepafenac.12,13 Furthermore, it has been shown that verteporfin photodynamic therapy (PDT) effectively slows vision loss in neovascular AMD through a photo-angio-occlusion mechanism.14,15 Because verteporfin PDT and ranibizumab target different disease components of CNV, combination therapy has been shown to require fewer IVR injections over 12 months.16,17

To further explore these combination therapies, we performed a 12-month, open-label, randomized prospective study to compare the effectiveness of 3 different arms of treatment over a 12-month follow-up period in patients with AMD complicated by CNV: 1) IVR, 2) IVR plus ketorolac eye drops, and 3) IVR plus loading-phase reduced-fluence (RF) verteporfin PDT.

Patients and Methods

Study Design

This multicenter, open-label, pilot study in naïve eyes affected by neovascular AMD was conducted according to the ethical principles of the Declaration of Helsinki and was approved by the appropriate ethics committee. All study participants provided written informed consent.

Participants

Overall, 75 consecutive patients were enrolled over a 6-month period at the Eye Clinic of the University Hospital of Brescia (Spedali Civili di Brescia) and Naples (Primo Policlinico di Napoli) and were randomized into 1 of 3 groups at a ratio of 1:1:1. Group 1 (n = 25) received ranibizumab monotherapy (RM group), Group 2 (n = 25) received ranibizumab along with off-label topical ketorolac eye drops (ranibizumab plus ketorolac [RK] group) 3 times a day, and Group 3 (n = 25) received 1 session of RF verteporfin PDT followed by ranibizumab (RV group). All patients received monthly treatment with IVR (0.5 mg) for 3 months, followed by monthly pro re nata IVR to treat any residual disease.

Participants were evaluated on a monthly basis, and all the data were recorded in case report forms by an experienced study coordinator.

Inclusion and Exclusion Criteria

Subjects were eligible for this study if the following criteria were met: 1) provision of written informed consent and compliance with study assessments for the full duration of the study, 2) older than 40 years, and 3) presence of treatment-naive neovascular AMD. The inclusion criteria for AMD were neovascularization, fluid, or hemorrhage under the fovea. To establish the presence of new active CNV, we required evidence of leakage on fluorescein angiography and fluid on spectral-domain optical coherence tomography (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany), located either within or below the retina or below the retinal pigment epithelium. Neovascular AMD was diagnosed by one investigator (A.R.) and independently confirmed by a second investigator (L.D.).

The exclusion criteria were as follows: 1) any previous intravitreal treatment, 2) previous laser treatment in the study eye, 3) myopia > 7 diopters in the study eye, 4) concurrent eye disease in the study eye that could compromise visual acuity (e.g., diabetic retinopathy and advanced glaucoma), 5) concurrent corneal epithelial disruption or any condition that would affect the ability of the cornea to heal, and 6) known sensitivity to any component of the formulations being investigated.

Study Treatments

The treatment schedule is summarized in Figure 1. Patients in all the groups received an initial dose of 0.5 mg IVR, followed by 2 additional monthly injections. Retreatment criteria for further injections performed by a masked examiner were as follows: 1) any intraretinal or subretinal fluid upon optical coherence tomography, 2) new or persistent hemorrhage, and 3) decreased visual acuity as compared with the results of the previous examination. In the absence of fluid upon optical coherence tomography or visual acuity deterioration, fluorescein leakage of >25% of the lesion circumference or expansion of CNV was required for retreatment.

Patients in RK were given a bottle of eyedrops for self-administration of 0.45% ketorolac ophthalmic solution, which was provided free of charge by the company (Acular; Allergan, Irvine, CA). Ketorolac
was administered at a dose of 1 drop in the study eye, 3 times a day, over the 12-month study period. To monitor and enhance compliance, patients were asked to bring their used bottles of ketorolac to each visit.

The patients in RV received, on Day 1, loading-phase RF verteporfin PDT (wavelength, 689 nm; dose, 25 J/cm²; light intensity, 300 mW/cm²), 15 minutes after the start of infusion, for 83 seconds. On the same day, ranibizumab (0.5 mg) was injected into the vitreous cavity a minimum of 1 hour after the start of verteporfin PDT.

Assessments

At each visit, the following assessments were performed by a certified examiner masked to the treatment assignment: 1) measurement of Early Treatment Diabetic Retinopathy Study best-corrected visual acuity (BCVA), 2) fully dilated slit-lamp ophthalmic examination, 3) measurement of CRT by optical coherence tomography, and 4) assessment of adverse ocular events (i.e., uncontrolled inflammation, endophthalmitis, retinal tear or detachment, ocular surface disorders, conjunctival hyperemia, eye irritation, eye pain, eye pruritus, eye redness, headache, and iritis). Fundus photography (fluorescein and indocyanine green angiography) was performed at baseline, 3 months, and 12 months, and at any monthly visit between 4 months and 11 months based on the retreatment criteria.

Choroidal neovascularization was categorized as follows: predominantly classic (>50% classic) or minimally classic (<50% classic).

Outcome Measures and End Points

The primary objectives of this study were 1) to assess the mean change in visual acuity of the enrolled eye as measured by the best-corrected Early Treatment Diabetic Retinopathy Study letter score and 2) to measure the mean change in CRT.

The secondary objectives were 1) to compare the number of needed ranibizumab retreatments over the 12-month period between the treatment groups, 2) to perform a subgroup analysis based on the CNV type, and 3) to report any adverse ocular events at 12 months.

Statistical Analysis

Descriptive statistics were used to present the demographic and ocular baseline characteristics. To determine whether the changes in BCVA and CRT were significantly different, repeated measures of analysis of variance with Greenhouse–Geisser correction were performed. A one-way analysis of variance was used to analyze the differences in visual acuity, CRT, and number of injections between the treatment arms. All statistical analyses were performed using SPSS software (version 20). P < 0.05 were considered significant.

Results

A total of 75 eyes of 75 patients met the study criteria and were enrolled and randomized into 3 groups: IVR alone (RM group, n = 25); IVR plus ketorolac eyedrops (RK group, n = 25); or loading-phase verteporfin PDT plus IVR (RV group, n = 25).

Table 1 shows the baseline demographic and clinical characteristics of the participants. Overall, the baseline demographics across the three groups were well-balanced, and no significant differences between the groups were found. All 75 patients completed the
study. Participants in RK did not report any instance of noncompliance caused by ocular side effects of 12 months of ketorolac use, 3 times a day.

**Visual Acuity**

A significant improvement in the mean BCVA score was observed in all treatment groups, with the largest mean change from baseline observed in the RK group (Figure 2). During the loading phase of the 3 monthly injections, the mean change ± standard error (SE) in BCVA improved rapidly from baseline to 3 months by −0.15 ± 0.03 logMAR (20/68 ± 20/300), −0.27 ± 0.04 logMAR (20/43 ± 20/227), and −0.15 ± 0.03 logMAR (20/68 ± 20/300) in the RM group, RK group, and RV group, respectively. The mean change ± SE in BCVA from baseline to 12 months was −0.14 ± 0.52 logMAR (20/73 ± 20/29) in RM, −0.25 ± 0.60 logMAR (20/46 ± 20/27) in RK, and −0.10 ± 0.30 logMAR (20/97 ± 20/40) in RV. At 12 months, the mean ± SE difference between RM and RK was 0.13 ± 0.06 logMAR (20/77 ± 20/155; P = 0.049), between RV and RK was 0.14 ± 0.06 logMAR (20/73 ± 20/155; P = 0.039), and between RM and RV was −0.01 ± 0.06 logMAR (20/879 ± 20/155; P = 0.984). Thus, RK showed better functional outcomes than ranibizumab monotherapy and ranibizumab plus verteporfin PDT about the change in BCVA from baseline to 12 months. Table 2 shows the changes in visual acuity at key time points.

**Central Macular Thickness**

A sustained and significant decrease in mean CRT ± SE from baseline was observed for the RM group (−125 ± 15.2 μm; P < 0.0001), the RK group (−141 ± 20.5 μm; P < 0.0001), and the RV group (−130 ± 15.4 μm; P < 0.0001) from baseline to 12 months. At 12 months, the mean ± SE difference between RM and RK was 35.8 ± 10.2 μm (P = 0.002), between RM and RV was 5.54 ± 10.6 μm (P = 0.861), and between RV and RK was 30.3 ± 10.5 μm (P = 0.014). Thus, according to the change in CRT from baseline to 12 months, the RK treatment showed better anatomical outcomes than ranibizumab monotherapy or ranibizumab plus verteporfin PDT. CRT changes at key time points are shown in Table 2.

**Number of Injections**

The mean number of ranibizumab treatments needed was reduced in the RK (6.5 ± 1.2; P = 0.001) and RV (5.8 ± 1.3; P < 0.0001) groups compared with the RM group (7.8 ± 1.0). However, no significant differences were observed between the 2 combination treatments (P = 0.089).

**Subgroup Analysis**

The outcomes were evaluated prospectively in subgroups according to the CNV type. The RV group showed a higher mean BCVA at 12 months for patients with classic/predominantly classic CNV, although the difference was not significant (P = 0.18). No other noteworthy differences were noted.

**Safety and Adverse Effects**

The safety profile of the 3 treatment arms was comparable at 12 months. The most frequently reported ocular adverse effects are shown in Table 3. No serious adverse effects were observed during the
study period; all adverse effects were mild to moderate. Although mild burning/stinging was reported more frequently in RK group, no significant difference existed in the number of adverse ocular effects experienced among the three groups.

Discussion

Although the pathogenesis of CNV is complex and multifactorial, it is known to be initiated by damage to the outer retinal cells and retinal pigment epithelium, which triggers a cascade of inflammatory and angiogenic responses that lead to neovascularization underneath the fovea.\textsuperscript{10} Although AMD is not considered a classic inflammatory disease, immunocompetent cells, such as macrophages and lymphocytes, are present in the chorioretinal tissues affected by AMD.\textsuperscript{19} The most critical aspect in the progression of maculopathy is parainflammation of the retinal and choroidal tissues, which is mediated by activation products such as C3a, C5a, and C5b-9 and leads to bystander cell lysis.\textsuperscript{20,21}

Given the multidimensional facets of AMD, it is reasonable to consider various combination treatments, including the combination of the gold standard anti-VEGF regimen with anti-inflammatory agents or vessel-occluding therapies.

We believe that the combination of IVR with ketorolac and that of IVR with RF verteporfin PDT have the potential to reduce the burden associated with monthly IVR injections, albeit with different synergistic mechanisms of action. Indeed, the results of this pilot study suggest that the addition of topical 0.45% ketorolac may result in a significant reduction in the 12-month CRT in patients with neovascular AMD, with a slightly significant BCVA gain over IVR monotherapy and IVR plus verteporfin PDT in the loading phase.

Although the evidence based on human clinical trials is less consistent than that from animal models,\textsuperscript{22,23} a favorable effect of additive topical NSAID and anti-VEGF therapy in CNV has been recently reported in three clinical trials.\textsuperscript{8,9,11} Anatomical improvements shown in these trials and the reduction in the number of needed IVR retreatments reported by Gomi et al are consistent with those of our study. In particular, the 6-month BCVA and CRT trend of RK group in our study is similar to that described by Russo et al.\textsuperscript{8} However, our longer (12-month) follow-up period allowed us to also observe a significant BCVA gain with the IVR plus ketorolac treatment over IVR monotherapy. Incidentally, in RK group, a greater initial CRT reduction was appreciable 2 months after the initiation of treatment, which probably resulted in the better 12-month outcome in visual acuity. Indeed, lower initial retinal thickness is associated with less photoreceptor inner segment/outer segment disruption after resolution of exudation.\textsuperscript{24}

Although the 12-month improvements in BCVA and CRT were similar between the RM and RV
groups, the latter group required fewer ranibizumab injections. These findings are consistent with the DENALI study \(^{16}\) and other previously published studies. \(^{17,25}\) PDT in the combination treatment causes a thrombotic occlusion of CNV lesions, including the more mature vessels that may not be sensitive to anti-VEGF drugs, as they quickly become enveloped by pericytes. \(^{26}\) Moreover, the simultaneous anti-VEGF treatment further suppresses neovascularization in the CNV and inhibits VEGF release after PDT. This process may alter the CNV such that the need for ranibizumab retreatments is delayed.

This synergy could further benefit from genotyping to target PDT to subpopulations of CNV patients who are more likely to respond, according to coagulation-factor gene polymorphisms that promote either thrombosis or fibrinolysis. \(^{27,28}\)

In contrast to the SUMMIT trials, we chose not to provide any additional RF PDT during the follow-up period to avoid any potential cumulative fovea damage. However, administration of PDT during the follow-up period may be advantageous for eyes that may not be responsive to anti-VEGF therapy alone, as recently reported by Tozer et al. \(^{29}\)

The decreased number of IVR injections associated with both combination therapies is a pivotal aspect of this study, considering that intravitreal injections may be associated with serious adverse events, including endophthalmitis, retinal tears, and retinal detachment.

Although topical ketorolac is reportedly used 2 to 4 times a day, \(^{13,30}\) we decided to administer ketorolac 3 times a day to obtain the best effect/compliance ratio. No serious adverse events were reported in our study. The safety results show that the treatments were well tolerated in all groups, with a safety profile comparable with that observed in previous studies. Furthermore, compliance with eye drop use was very high, and the reported adverse events were of mild-to-moderate severity.

Subgroup analysis according to CNV type suggested that the classic or predominantly classic type of CNV is associated with a better 12-month BCVA outcome, although the difference was not statistically significant. This association has been demonstrated previously \(^{31,32}\) with verteporfin PDT treatment alone; it was also confirmed by the results of this study in which verteporfin PDT was administered in addition to ranibizumab.

To the best of our knowledge, this is the first pilot study reporting a better BCVA outcome with the addition of 0.45% ketorolac eyedrops, 3 times a day, to the IVR regimen in patients with neovascular AMD. As this was only a pilot study, additional studies using a larger sample size and longer follow-up period are

### Table 2. Changes in Visual Acuity and CRT at Key Time Points

|                  | Baseline | 2 months | 4 months | 6 months | 8 months | 10 months | 12 months |
|------------------|----------|----------|----------|----------|----------|-----------|-----------|
| **VA (mean ± SD)** |          |          |          |          |          |           |           |
| RM group (logMAR) | 0.61 ± 0.30 | 0.47 ± 0.28 | 0.46 ± 0.28 | 0.44 ± 0.25 | 0.45 ± 0.23 | 0.48 ± 0.28 | 0.49 ± 0.27 |
| Snellen equivalent | 20/102 ± 67 | 20/72 ± 50 | 20/77 ± 57 | 20/64 ± 43 | 20/71 ± 39 | 20/65 ± 33 | 20/70 ± 28 |
| RK group (logMAR) | 0.68 ± 0.34 | 0.54 ± 0.22 | 0.49 ± 0.16 | 0.44 ± 0.19 | 0.49 ± 0.23 | 0.55 ± 0.27 | 0.58 ± 0.25 |
| Snellen equivalent | 20/100 ± 62 | 20/72 ± 50 | 20/77 ± 57 | 20/64 ± 43 | 20/71 ± 39 | 20/65 ± 33 | 20/70 ± 28 |
| RV group (logMAR) | 0.69 ± 0.34 | 0.54 ± 0.22 | 0.49 ± 0.16 | 0.44 ± 0.19 | 0.49 ± 0.23 | 0.55 ± 0.27 | 0.58 ± 0.25 |
| Snellen equivalent | 20/100 ± 62 | 20/72 ± 50 | 20/77 ± 57 | 20/64 ± 43 | 20/71 ± 39 | 20/65 ± 33 | 20/70 ± 28 |
| CRT (mean ± SD) |          |          |          |          |          |           |           |
| RM group (µm) | 440 ± 84 | 339 ± 87 | 340 ± 87 | 340 ± 87 | 340 ± 87 | 340 ± 87 | 340 ± 87 |
| RK group (µm) | 420 ± 87 | 318 ± 43 | 315 ± 43 | 315 ± 43 | 315 ± 43 | 315 ± 43 | 315 ± 43 |
| RV group (µm) | 439 ± 74 | 313 ± 35 | 313 ± 35 | 313 ± 35 | 313 ± 35 | 313 ± 35 | 313 ± 35 |
warranted to validate the results of our study, especially considering the recent findings of the SEVEN-UP study that reported a risk of substantial visual decline even during the late stages of neovascular AMD.\(^3\)

In conclusion, combination therapy with loading-phase RF verteporfin PDT and ranibizumab may be useful in some patients with CNV because it has the potential to decrease the number of IVR injections needed, thereby decreasing the overall treatment burden. Topical 0.45% ketorolac administered off-label 3 times a day acts synergistically with IVR, offering valuable therapeutic support to IVR in patients eligible for long-term use of topical NSAIDs.

**Key words:** choroidal neovascularization, combination therapy, ketorolac eyedrops, photodynamic therapy, ranibizumab injections.

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