DOSING REGIMEN AND THE FREQUENCY OF MACULAR HEMORRHAGES IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TREATED WITH RANIBIZUMAB

IRENE BARBAZETTO, MD,* NAMRATA SAROJ, OD,† HOWARD SHAPIRO, PHD,† PAMELA WONG, MPH,† K. BAILEY FREUND, MD*

Purpose: The purpose of this study was to investigate if monthly intravitreal ranibizumab decreases risk of macular hemorrhages in patients with choroidal neovascularization secondary to age-related macular degeneration.

Methods: Incidences of macular hemorrhages in the control and ranibizumab groups from three, multicenter, randomized, clinical trials (MARINA, ANCHOR, and PIER) were compared. Two time intervals (Months 0–3 and 5–17) were evaluated to account for transition from monthly to quarterly injections in PIER. Time interval after Month 17 was excluded because of crossover from control to active treatment in all trials.

Results: Months 0–3: All trials showed higher incidence rates of hemorrhages in control compared with ranibizumab groups (ANCHOR: photodynamic therapy [27.3%], 0.3 mg [8.0%], 0.5 mg [8.6%]; MARINA: sham [18.6%], 0.3 mg [8.8%], 0.5 mg [8.8%]; and PIER: sham [16.1%], 0.3 mg [3.4%], 0.5 mg [3.3%]). In ANCHOR and MARINA, data of Months 5–17 showed higher incidence rates in control compared with monthly ranibizumab groups (ANCHOR: photodynamic therapy [47.8%], 0.3 mg [12.5%], 0.5 mg [12.3%]; and MARINA: sham [38.0%], 0.3 mg [13.2%], 0.5 mg [13.0%]), but this was not seen for quarterly ranibizumab groups in PIER (sham [22.4%], 0.3 mg [23.7%], 0.5 mg [28.3%]).

Conclusion: Treatment with monthly intravitreal ranibizumab was associated with reduced risk of new macular hemorrhages when compared with photodynamic therapy (ANCHOR) or sham (MARINA and PIER). There was no difference between PIER quarterly ranibizumab-treated and sham patients.

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Macular hemorrhages are considered to be a hallmark of neovascular age-related macular degeneration (AMD). Reading centers use the presence of subretinal hemorrhages or hemorrhagic pigment epithelial detachments as a criteria for the presence of choroidal neovascularization[1] when grading fundus photographs of patients with AMD in the absence of other imaging modalities such as fluorescein angiography or optical coherence tomography. Even intraretinal hemorrhages can be a sign of serious progression because they have been associated with the early stages of retinal angiomatous proliferation/type 3 neovascularization.[2] Overall, macular hemorrhages are considered to be a sign of disease activity and, when occupying larger areas or located in the subfoveal region, they are usually associated with a poor visual prognosis in a majority of cases.[3–5] Therefore, prevention or suppression of hemorrhagic incidences should help arrest vision loss.

Intravitreal antivascular endothelial growth factor therapy has become the new standard of care for treating neovascular AMD. This therapy has not only changed the management of neovascular AMD but also, for the first time, improved visual function and limited disease activity in the majority of patients for at least two years.[6,7] Thus, it seems reasonable to believe that

frequent treatment could also potentially limit the occurrence of macular hemorrhages in these patients.

The aim of this exploratory analysis of the data from three Phase 3 clinical trials was to investigate if monthly treatment with intravitreal ranibizumab (Lucentis; Genentech Inc., South San Francisco, CA) decreases the risk of new macular hemorrhages in patients with choroidal neovascularization secondary to AMD.

Material and Methods

An exploratory analysis was conducted using the 2-year safety data from patients enrolled in three, Phase 3, randomized, controlled, multicenter, clinical trials: MARINA,[6] ANCHOR,[7,8] and PIER.[9] Safety-evaluable population included all patients who received at least one study treatment.

Treatment and Follow-up

In MARINA, patients were randomized to sham control or monthly intravitreal ranibizumab injections of 0.3 mg or 0.5 mg. Patients in the ANCHOR study were assigned to verteporfin photodynamic therapy (PDT) (plus monthly sham injections) control or monthly intravitreal ranibizumab injections of 0.3 mg or 0.5 mg (plus sham PDT with saline infusion). In PIER, patients were randomized to sham control or intravitreal ranibizumab injections of 0.3 mg or 0.5 mg. Patients received 3 initial monthly treatments of their assigned dose followed by treatment every 3 months.

In all 3 studies, patients were examined at screening and Day 0. In MARINA and ANCHOR, patients were seen at Day 7 and then monthly from Month 1 through Month 24. In PIER, patients were examined monthly through Month 3 and quarterly starting at Month 5 through Month 23 with additional visits at Months 12 and 24. There was no Month 4 visit in the PIER study. At all study visits, patients were evaluated using Early Treatment Diabetic Retinopathy Study protocol–based best-corrected visual acuity, slit-lamp examination, intraocular pressure measurement, and dilated binocular indirect and high-magnification ophthalmoscopy. Adverse events were collected at every visit except at screening. Fluoroscein angiography and fundus photography were performed at screening and at Months 3, 6, 12, and 24 in MARINA, every 3 months starting at screening up to 24 months in ANCHOR, and at screening and at Months 3, 5, 8, 12, and 24 in PIER. In MARINA and ANCHOR, optical coherence tomography was done at select sites at Days 0 and 7 as well as at Months 1 and 12. In PIER, optical coherence tomography was done at select sites at Day 0 and at Months 1, 2, 3, 5, 8, and 12.

Data Collection

The incidences of new macular hemorrhages detected during these studies were identified based on verbatim reports by the study investigators. All verbatim adverse event descriptions coded to the MEDDRA (Medical Dictionary of Regulatory Activities) preferred term: ''RETINAL HEMORRHAGE'' in the databases were reviewed by the authors (I.B., K.B.F., and N.S.) and reclassified to three categories (''Yes,'' ''Maybe,'' and ''No'') on whether they were macular hemorrhages. Only events coded with ''Yes'' or ''Maybe'' were included in the final analysis (Table 1).

To account for the transition from monthly injections to quarterly injections in the PIER trial after 3 months, the number of events in all studies was evaluated for 2 time intervals: 0 to 3 months (during monthly injections in MARINA, ANCHOR, and PIER) and 5 to 17 months (during monthly injections in MARINA and ANCHOR and quarterly injections in PIER). The 5- to 17-month time interval was further broken down into quarterly intervals: 5 to <8 months, 8 to <11 months, 11 to <14 months, and 14 to 17 months. The time interval between 3 and 5 months

Table 1. Included cases for ''macular hemorrhage'' based on investigator verbatim report coded to the MedDRA (Medical Dictionary for Regulatory Activities) preferred term: ''RETINAL HEMORRHAGE''

New subretinal hemorrhage
Punctate hemorrhage – subretinal
Hemorrhagic pigment epithelial detachment
Peripapillary subretinal hemorrhage
Recurrent subretinal hemorrhage
Worsening of subretinal macular hemorrhage
Macular dot-blot hemorrhage

From the *Vitreous Retina Macula Consultants of New York, New York, New York; and †Genentech Inc., South San Francisco, California.

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K.B. Freund is a consultant for Genentech. P. Wong, N. Saroj and H. Sahpiro are employees of Genentech.

The study protocols of the ANCHOR, MARINA, and PIER trials (primary reports of safety and efficacy published previously[6–9]) were approved by the Institutional Review Board, National Competent Authority, or Ethics Committee at each participating clinical center before the start of the study. All US sites were compliant with the Health Insurance Portability and Accountability Act of 1996. The three studies are registered at ClinicalTrials.gov (ANCHOR ID No. = NCT0061594; MARINA ID No. = NCT00056836; PIER ID No. = NCT00090623). Before determination of their full eligibility for enrollment, all patients provided written informed consent for their study participation.

Reprint requests: K. Bailey Freund, MD, Vitreous Retina Macula Consultants of New York, 460 Park Avenue, 5th Floor, New York, NY 10022; e-mail: kbfnyf@aol.com

was excluded because there was no Month 4 study visit in the PIER trial. The time interval after Month 17 was excluded because control patients remaining in the studies were allowed to ''crossover'' to receive ranibizumab in all 3 studies, and many patients switched to monthly 0.5 mg during this period in PIER. However, all adverse events occurring after the crossover were excluded from the analysis.

Statistical Analysis

Incidences of macular hemorrhages were compared using Pearson chi-square or Fisher exact test (when expected cell counts <5) for treatment comparisons within each study as well as cross-study comparisons within each treatment group. These cross-study comparison tests were performed not for formal comparison but for hypothesis generation only. Statistical significance was defined as $P < 0.05$; although in an exploratory analysis, it is particularly important to consider the risks of false conclusions due to multiple comparisons. All statistical analyses were carried out using SAS software v9.1 (SAS Inc, Cary, NC).

Subgroup Analyses

The influence of selected variables was explored in three separate subgroup analyses comparing the incidences of macular hemorrhages: 1) by baseline angiographic lesion composition, presence of classic (either predominantly classic or minimally classic) versus occult lesions in MARINA and PIER; 2) by baseline presence or absence of anticoagulation/platelet inhibitors; and 3) by baseline presence or absence of blood on fluorescein angiography.

Results

A total of 1,315 patients receiving at least 1 study treatment were analyzed from the 3, randomized, controlled, clinical trials: ANCHOR (n = 420), MARINA (n = 713), and PIER (n = 182). The sample size of each study for the evaluated treatment intervals and study arms is shown in Figure 1.

Incidences of Macular Hemorrhages

Months 0–3: monthly ranibizumab or sham injection. In all 3 trials, a higher percentage of patients developed macular hemorrhages in the control group compared with both the ranibizumab-treated groups during Months 0 to 3. In the ANCHOR trial (Figure 1A), new macular hemorrhages were seen in 27.3% of PDT-treated eyes compared with 8.0% in the 0.3-mg ranibizumab-treated group ($P < 0.0001$) and 8.6% in the 0.5-mg ranibizumab-treated group ($P < 0.0001$).

The MARINA trial (Figure 1B) showed 18.6% in the sham group developing macular hemorrhages compared with 8.8% in the 0.3-mg ranibizumab-treated group ($P = 0.0019$) and 8.8% in the 0.5-mg ranibizumab-treated group ($P = 0.0018$).

In the PIER trial (Figure 1C), 16.1% in the sham group and 3.4% in the 0.3-mg ranibizumab-treated group ($P = 0.019$) and 3.3% in the 0.5-mg ranibizumab-treated group ($P = 0.016$) developed macular hemorrhages.

Months 5–17: monthly ranibizumab or sham injection (MARINA/ANCHOR); quarterly ranibizumab or sham injection (PIER). During Months 5 to 17, the incidence of macular hemorrhages was still higher in the control groups for ANCHOR and MARINA when compared with the ranibizumab-treated groups. The ANCHOR trial (Figure 1, Panel D) had 47.8% of PDT treated patients compared to 12.5% in the 0.3 mg ranibizumab-treated group ($P < 0.0001$) and 12.3% in the 0.5 mg ranibizumab-treated group ($P < 0.0001$) develop a macular hemorrhage. The MARINA trial (Figure 1E) also showed a higher rate of new macular hemorrhages in the sham group with 38.0% compared with lower rates of 13.2% in the 0.3-mg ranibizumab-treated group ($P < 0.0001$) and 13.0% in the 0.5-mg ranibizumab-treated group ($P < 0.0001$).

However, in the PIER trial (Figure 1F), the incidence rates were not lower in the ranibizumab-treated groups compared with the control group (in fact, they were slightly higher although the differences were not statistically significant). 22.4% of patients in the sham group developed new macular hemorrhages when compared with 23.7% in the 0.3-mg ranibizumab-treated group ($P = 0.87$) and 28.3% in the 0.5-mg ranibizumab-treated group ($P = 0.46$).

For quarterly incidences of new macular hemorrhages in the ANCHOR (Figure 2A) and MARINA (Figure 2B) studies after Month 5, the rate in the ranibizumab-treated groups appears stable between 1% and 7%, whereas the control groups (sham/PDT) range from 10% to 22%. In the PIER study (Figure 2C), the overall incidence of new macular hemorrhages ranged from 3% to 17% for the ranibizumab-treated eyes and from 4% to 10% for the control (sham) eyes.

Cross-Study Comparison Between Studies

Given the different patient populations; different control groups; and differences in sample size, follow-up, and crossover regimens, cross-study comparisons (Figure 1) are intended for hypothesis generation only and the data should be reviewed with caution. As a reference (not for formal comparisons), Pearson chi-square or Fisher exact test (when expected cell counts <5) yields the following P values for cross-study

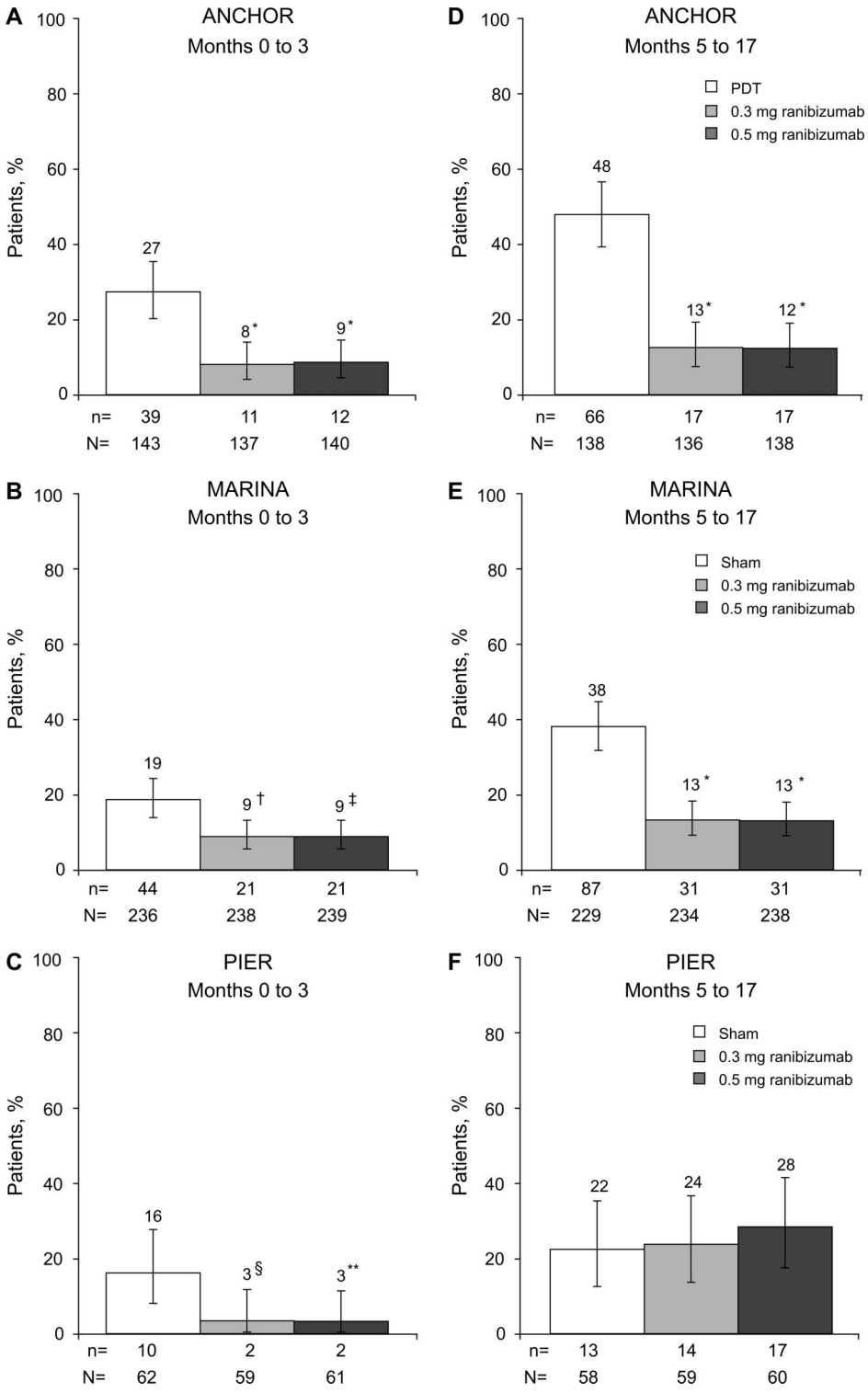

Fig. 1. Summary of the incidences of new macular hemorrhages in the study eye in the ANCHOR (**A** & **D**), MARINA (**B** & **E**) and PIER (**C** & **F**) studies subdivided for the 2 study periods (months 0–3 and months 5–17). *$P < 0.0001$, †$P = 0.0019$, ‡$P = 0.018$ §$P = 0.019$, **$P = 0.016$ vs. control (sham or PDT). Error bars are 95% exact confidence intervals.

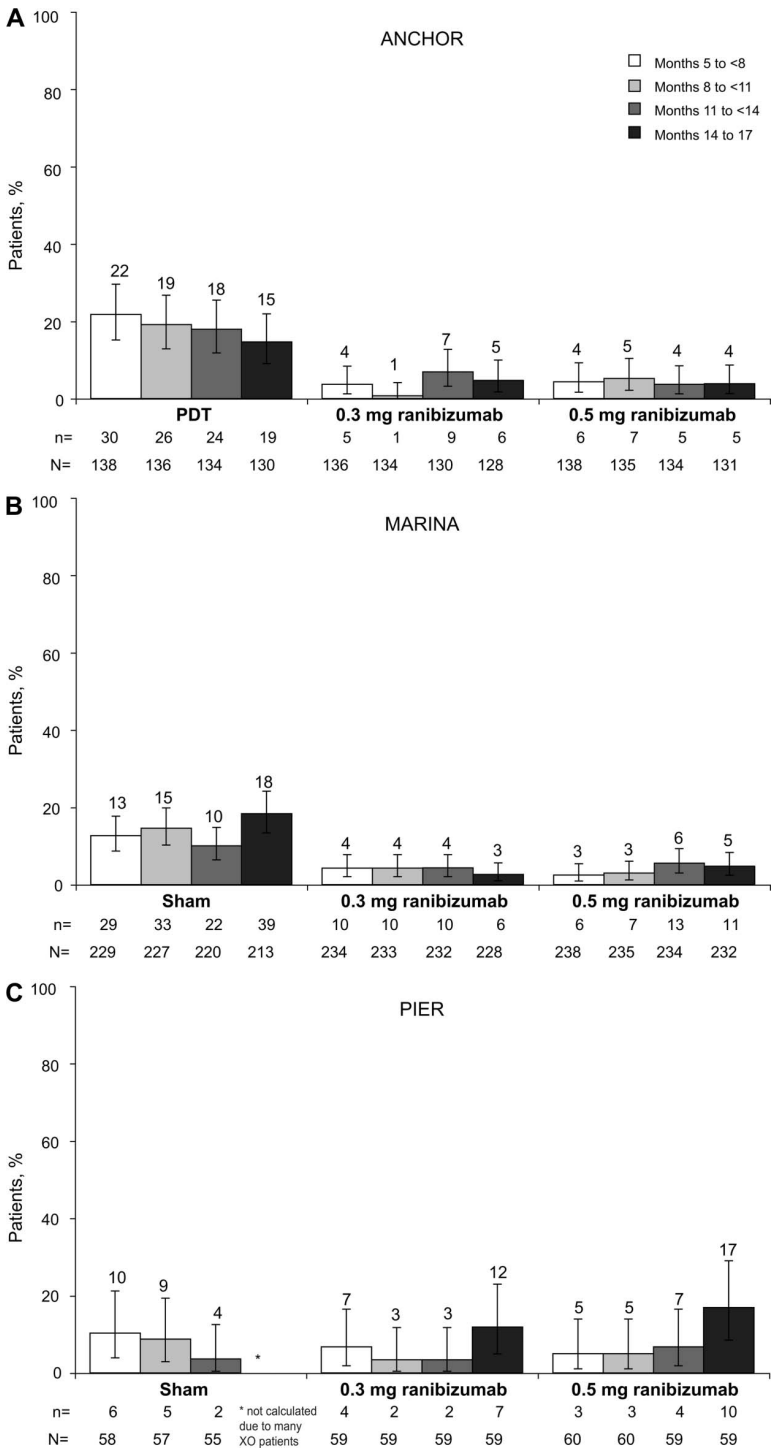

Fig. 2. Quarterly reported incidences of new macular hemorrhages in the ANCHOR (**A**), MARINA (**B**), and PIER (**C**) studies, Months 5 to 17. *Months 14 to 17 for the PIER sham group were excluded from the summary because most patients in sham crossed over to receive 0.5-mg ranibizumab at Month 14. Error bars are 95% exact confidence intervals.

comparison for the incidence of macular hemorrhages within each treatment group.

For the Months 0 to 3 interval, little difference was found between the incidence rates in the PIER and MARINA trials (control [$P = 0.65$], 0.3 mg [$P = 0.27$], and 0.5 mg [$P = 0.18$]). Similarly, little difference was found between the incidence rates in PIER and ANCHOR trials (control [$P = 0.09$], 0.3 mg [$P =$

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