MARINA and ANCHOR: An Overview of the Safety Data

Combined 2-year analysis increases confidence in ranibizumab.

BY CARL REGILLO, MD

Today, retinal specialists have the benefit of having antivascular endothelial growth factor (VEGF) agents to treat their patients with age-related macular degeneration (AMD). Regardless of the benefits that a drug offers patients, however, the potential for good outcomes will always be tempered by a concern for side effects. Since the approval of ranibizumab (Lucentis, Genentech) retinal specialists have enjoyed the visual benefits that the drug provides; however, they have at the same time eagerly awaited the long-term safety data from several trials.

The MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) trials independently showed possible safety signals, raising some degree of concern about possible systemic side effects of ranibizumab. In this article, I will review the combined safety data from MARINA and ANCHOR, focusing on systemic safety issues that had been of some concern.

TRIAL DESIGN DIFFERENCES

The MARINA trial was designed as a phase 3, randomized, multicenter, double-masked, sham-controlled study enrolling 716 patients with minimally classic lesions or occult with no classic lesions. Patients were randomized 1:1:1 to either sham (n=238), ranibizumab 0.3 mg (n=238), or ranibizumab 0.5 mg (n=240). The ANCHOR trial, also a phase 3 randomized, multicenter, double-masked study, was designed as an active treatment-controlled study. All of the patients in the study (n=423) had predominantly classic lesions. Randomization was 1:1:1 with 143 patients assigned to

TABLE 1: KEY ELIGIBILITY CRITERIA

Study	Lesion Characteristics	Other Criteria
MARINA	• Minimally classic or occult with no classic • Choroidal neovascularization (CNV) • Total area of CNV must be ≥50% of total lesion area • Evidence of presumed recent disease progression (eg, blood, recent growth by fluorescein angiography, or recent visual acuity loss) • Lesion size ≤12 disc areas (DA)	• Age ≥50 years • No prior PDT • Subfoveal CNV secondary to AMD • Visual acuity (Snellen equivalent) 20/40 to 20/320 • Patients with prior cardiovascular events were not excluded
ANCHOR	• Predominantly classic CNV • Total lesion 5400 µm in greatest linear dimension (~9 DAs)	• Age ≥50 years • No prior PDT • Subfoveal CNV secondary to AMD • Visual acuity (Snellen equivalent) 20/40 to 20/320 • Patients with prior cardiovascular events were not excluded

TABLE 2. OCULAR SERIOUS ADVERSE EVENTS

MARINA + ANCHOR (COMBINED)

	Year 1 (final study database)			Year 2 - Cumulative		
		Ranibizumab			Ranibizumab	
	Control * (n=379)	0.3 mg (n=375)	0.5 mg (n=379)	Control * (n=379)	0.3 mg (n=375)	0.5 mg (n=379)
Presumed Endophthalmitis†						
• Culture positive	0	0	1 (0.3%)	0	0	1 (0.3%)
• Culture negative	0	0	2 (0.5%) ‡	0	1 (0.3%)	4 (1.1%) ‡
• Culture not done	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	1 (0.3%) §
Uveitis	0	2 (0.5%)	2 (0.5%)	0	3 (0.8%)	4 (1.1%)§**
Rheg. retinal detachment	1 (0.3%)††	1 (0.3%)††	0	2 (0.5%)††	2 (0.5%)	0
Retinal tear	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	2 (0.5%)
Vitreous hemorrhage	0	2 (0.5%)	1 (0.3%)	2 (0.5%)	3 (0.8%)	1 (0.3%)
Lens damage	0	0	1 (0.3%)	0	0	1 (0.3%)

** Sham injection-control for MARINA and active treatment-control with verteporfin PDT for ANCHOR*

† Defined as cases reported as endophthalmitis or uveitis in which intravitreal or systemic antibiotics were administered

‡ One case was reported as uveitis

§ One patient was reported as having 2 episodes of uveitis in 1st treatment year and was treated with systemic antibiotics for the 1st episode. A vitreous culture was not done.

*** One patient had two episodes of uveitis and was discontinued after the 2nd episode*

†† One patient had 2 episodes

CVA=cerebrovascular accident (including stroke)

CHF=congestive heart failure

NHL=non-Hodgkin's lymphoma

CAD=coronary artery disease

TABLE 3. KEY SYSTEMIC SAFETY FINDINGS POTENTIALLY RELATED TO VEGF-A INHIBITION

	MARINA + ANCHOR (Combined)					
	Year 1 (final study database)			Year 2 - Cumulative		
		Ranibizumab			Ranibizumab	
	Control (n=379)	0.3 mg (n=375)	0.5 mg (n=379)	Control (n=379)	0.3 mg (n=375)	0.5 mg (n=379)
Deaths						
• Nonvascular	1 (0.3%)	2 (0.5%)	1 (0.3%)	4 (1.1%)	5 (1.3%)	4 (1.1%)
• Vascular*	1 (0.3%)	2 (0.5%)	3 (0.8%)	7 (1.8%)	5 (1.3%)	5 (1.3%)
Nonfatal MI*	2 (0.5%)	3 (0.8%)	4 (1.1%)	6 (1.6%)	7 (1.9%)	8 (2.1%)
Nonfatal CVA*	2 (0.5%)	2 (0.5%)	3 (0.8%)	4 (1.1%)	6 (1.6%)	6 (1.6%)
Hypertension	38 (10.0%)	24 (6.4%)	34 (9.0%)	61 (16.1%)	54 (14.4%)	56 (14.8%)
Mean change in SBP/DBP (mmHg) at month 12/24†	-1/1	-1/2	-4/0	-4/-3	-2/-2	-4/-1
Proteinuria	0	0	0	1 (0.3%)	0	0
Nonocular hemorrhage‡	13 (3.4%)	16 (4.3%)	13 (3.4%)	20 (5.3%)	34 (9.1%)	34 (9.0%)

** Antiplatelet Trialists' Collaboration (APTC) Arterial Thromboembolic Events. Antiplatelet Trialists Collaboration, BMJ. 1994308(6921):81 used during FDA COX-2 inhibitor advisory panel meetings Feb'05.*

† N's vary because not all patients had their blood pressure taken at 12 and 24 months

‡ Includes epistaxis, hematuria, ecchymosis, hematoma, GI hemorrhage, subdural hematoma, duodenum ulcer hemorrhage, hematemesis, subarachnoid hemorrhage, etc

CVA=cerebrovascular accident (including stroke)

CHF=congestive heart failure

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PDT, 140 patients to treatment with ranibizumab 0.3 mg, and 140 patients to ranibizumab 0.5 mg. The key eligibility criteria for both MARINA and ANCHOR are seen in Table 1.

In common to both studies was the diagnosis of age-related macular degeneration (AMD) and subfoveal choroidal neovascularization (CNV) with identical patient age and visual criteria. No prior photodynamic therapy (PDT) was allowed in either study. It is important to note, however, that there were no exclusionary criteria in either study for prior cardiovascular events. The CNV lesion size at study entry was smaller in ANCHOR to accommodate possible PDT. Recent disease progression was required in MARINA.

METHODS

The combined safety analysis included a total of 754 patients treated with ranibizumab in the phase 3 MARINA and ANCHOR trials. There were a total of 9,242 ranibizumab and 4,476 sham injections in year 1 and 16,364 ranibizumab injections and 7,443 sham injections through year 2. The number of ranibizumab injections excluded injections for sham (MARINA) and PDT (ANCHOR) crossover patients in the second year. Crossover for the MARINA study occurred at approximately 20 months for 12 patients and approximately 18 months for 50 patients in the ANCHOR study.

Patients received their first injection on day 0 of the study and therefore had 13 injections in year 1 and 11 in year 2.

OCULAR SERIOUS ADVERSE EVENTS

Table 2 shows the ocular serious adverse events from both studies together out through 2 years. It is important to note that the percentages shown are per-patient event rates, not per-injection.

The occurrance of ocular serious adverse events through year 2 was uncommon. The occurrence of any single ocular adverse event (eg, endophthalmistis, uveitis, vitreous hemorrhage) was lower than 1.6%, comparable to other pharmacotherapeutics administered by intravitreal injection.

SYSTEMIC SAFETY DATA

Perhaps of greater interest are the key systemic serious adverse events (Table 3) possibly related to an anti-VEGF effect. In year 1 of the MARINA study, there was some concern that there was a higher incidence of cerebrovascular accident (CVA) in the treatment arm. In years 1 and 2 of the ANCHOR study, there was a slight increase in myocardial infarction (MI) in the ranibizumab treatment arms. There was no imbalance, however, in the combined analysis with regard to deaths, CVA, or MI.

> The 1-year data [from SAILOR] showed however, that there was no significant risk for patients receiving the higher dose [of ranibizumab].

One adverse event that did show as a trend was nonocular hemorrhaging in the 2-year combined data. Nonocular hemorrhaging occurred in 5.3% of the control groups and in 9.1% and 9.0% in the 0.3 mg and 0.5 mg ranibizumab groups, respectively. The nonocular hemorrhaging events, however, were not separated according the seriousness of the events.

By end of study, no imbalance in deaths was evident. In year 1, there were no deaths in the sham group. While not as apparent in the first year, throughout the study there was a mix of etiologies for death — only some of which may be related to systemic anti-VEGF activity. This further demonstrates the need for larger patient groups and longer follow-up times to sort out apparent trends.

NEW DATA ON SAFETY

Recently, David Boyer, MD, presented the 1-year data from the phase 3b SAILOR (Safety Assessment of Intravitreal Lucentis for AMD) trial. These data showed that the US Food and Drug Administration-approved dose of ranibizumab (0.5%) was safe and not associated with any statistically significant higher risk of stroke compared with the 0.3 mg dose. These data answered the concern that was raised when, in January 2007, Genentech mailed letters to physicians notifying them of the possible safety signal found in the 6-month interim data. In those data, patients with previous risk for stroke appeared to be at higher risk. The 1-year data showed, however, that there was no significant risk for patients receiving the higher dose (P=.21).

These 1-year data from SAILOR, along with the combined 2-year combined safety analysis of MARINA and ANCHOR, serve to increase the confidence that retinal specialists have in ranibizumab as a safe, effective therapy for AMD. ■

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