

RESEARCH LETTER

Interim Safety Data Comparing Ranibizumab With Panretinal Photocoagulation Among Participants With Proliferative Diabetic Retinopathy

Protocol S of the Diabetic Retinopathy Clinical Research Network (clinicaltrials.gov [NCT01489189](#)) compares intravitreal ranibizumab vs panretinal photocoagulation (PRP) for managing proliferative diabetic retinopathy.

Methods | Participants with 1 eye used in the study were randomly assigned to a dose of 0.5 mg ranibizumab (n = 102) or PRP (n = 114); participants with 2 eyes in the study (n = 89) had 0.5 mg of ranibizumab administered in 1 eye and PRP in the other eye (total 394 study eyes). If treatment also was required for diabetic macular edema, according to the protocol, eyes were treated with 0.5 mg of ranibizumab regardless of the treatment group assignment. The primary efficacy analysis showed that the mean change in visual acuity from baseline at 2 years among the ranibizumab group was noninferior compared with (not worse than) the group who underwent PRP. Based on visual acuity and secondary outcomes that favor ranibizumab, anti-vascular endothelial growth factor therapy could be considered as an alternative to PRP. Data through the 2-year primary outcome did not raise any systemic safety concerns.¹ The trial is continuing to collect efficacy and safety data for 5 years until 2018.

The primary prespecified systemic safety outcomes were all-cause death, serious adverse events, hospitalizations, and the following cardiovascular/cerebrovascular events defined

by the Antiplatelet Trialists' Collaboration²: nonfatal myocardial infarction, nonfatal stroke, and death attributed to a cardiac, cerebral, hemorrhagic, embolic, or other vascular disorder or of an unknown cause.

While reviewing all available data at a monitoring meeting that coincided with approximately 90% of active participants having completed the 4-year visit, the study's Data and Safety Monitoring Committee noted a trend toward increased Antiplatelet Trialists' Collaboration events among participants assigned to ranibizumab treatment compared with undergoing PRP (Table). The statistical analysis plan specified that *P* values less than .01 would be considered statistically significant (to adjust for multiple comparisons). Although the observed *P* value was .10, the concern of the Data and Safety Monitoring Committee that this trend could be consistent with a possible increased Antiplatelet Trialists' Collaboration event rate among the ranibizumab group led the committee to recommend that study participants be informed of this trend. The Data and Safety Monitoring Committee also concluded that the results were not sufficiently indicative of an increased risk to warrant discontinuing the ranibizumab treatment. This study adhered to the tenets of the Declaration of Helsinki and was approved by multiple institutional review boards that are listed in Protocol S. Study participants provided written informed consent.

Results | There are many caveats when interpreting this information. Notably, 50% of the group who underwent PRP received ranibizumab for diabetic macular edema during the

Table. Prespecified Primary Safety Adverse Events^a

Proportion of Participants With ≥1 Event	Treatment Group, No. (%) ^b			<i>P</i> Value ^c
	Bilateral (n = 89)	Ranibizumab (n = 102)	Prompt PRP (n = 114)	
No. of study ranibizumab injections (No./participant)	1917 (21.5)	1527 (15.0)	438 (3.8)	
Death from any cause	7 (8)	11 (11)	6 (5)	.32
Hospitalization	47 (53)	63 (62)	57 (50)	.20
Serious adverse event ^d	52 (58)	67 (66)	62 (54)	.23
Any APTC event (any of the following) ^e	11 (12)	18 (18)	9 (8)	.10
Nonfatal myocardial infarction	3 (3)	7 (7)	3 (3)	.31
Nonfatal stroke	3 (3)	6 (6)	4 (4)	.64
Death from vascular or unknown cause	5 (6)	6 (6)	2 (2)	.23

Abbreviations: APTC, Antiplatelet Trialists' Collaboration; PRP, panretinal photocoagulation.

^a Data received by the Coordinating Center through December 6, 2016.

^b The statistical analysis plan prespecified the conduct of the primary safety analyses in these 3 groups and prespecified a *P* value level of .01 for statistical significance as an adjustment for multiple comparisons.

^c Global *P* values are from Fisher exact testing of whether there is any difference among the 3 treatment arms.

^d Serious adverse event defined as any untoward occurrence that meets 1 or more of the following criteria: (1) results in death, (2) is life-threatening, (3)

requires inpatient hospitalization or a prolongation of an existing hospitalization, (4) results in persistent or significant disability/incapacity or a substantial disruption of the ability to conduct normal life functions, (5) is a congenital anomaly/birth defect, and (6) is considered to be a significant medical event by the investigator based on a medical judgment (eg, may jeopardize the participant or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

^e Antiplatelet Trialists' Collaboration events include nonfatal myocardial infarction, nonfatal stroke, and death attributed to cardiac, cerebral, hemorrhagic, embolic, or other vascular disorder or of unknown cause.

study; therefore, there was no control group without ranibizumab exposure. The 4-year retention rate is approximately 70%, excluding deaths. The Antiplatelet Trialists' Collaboration event rate among those lost to follow-up is unknown and cannot be accounted for in the analysis. Finally, the *P* values of the prespecified safety analyses all exceeded the prespecified significance level, indicating a reasonable possibility that the findings could be because of chance.

Discussion | Systemic intravenous antivasular endothelial growth factor therapy (eg, treating metastatic colon cancer³) has been reported to increase the risk of vascular events. Some prior publications suggest that intravitreal antivasular endothelial growth factor injections at dosages approximately 400 times smaller than cancer dosages could convey a small increased risk of systemic vascular events.⁴ Prior ocular studies have been inconclusive; some report a small increased risk while others suggest that there is no increased risk or that there is a decreased risk.⁵ An extensive analysis of Genentech/Novartis-sponsored randomized clinical trials evaluating ranibizumab treatment for diabetic macular edema,⁶ did not demonstrate an increased risk of systemic vascular events. However, a possible risk of cardiovascular events is noted in the ranibizumab package insert and was included in the patient informed consent for the Diabetic Retinopathy Clinical Research Network Protocol S study.

Because Diabetic Retinopathy Clinical Research Network is informing Protocol S participants about the trend toward increased cardiovascular events within the ranibizumab arm, the network believes it is important to make this information publicly available. However, network investigators remain uncertain about a possible association between increased cardiovascular events and the treatment of proliferative diabetic retinopathy with ranibizumab. A full report is planned on the completion of the 5-year follow-up in 2018.

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OBSERVATION

Ocular Chemical Burns Secondary to Unintentional Instillation of Aqua Regia Hobbyist Reagent: Not All That Glitters Is Gold

We report 2 cases of unintentional ocular self-administration of aqua regia, a mixture of hydrochloric and nitric acids, used by hobbyists to determine gold purity. Aqua regia is commercially available and supplied in 15-mL eyedrop bottles that resemble those containing pharmacologic eyedrops (Figure 1). This poses a patient safety hazard that may produce severe and irreversible acid burn injuries to the eye.

Report of Cases | *Case 1.* A 65-year-old woman on postoperative day 11 following an uncomplicated phacoemulsification and