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Systemic Vascular Safety of Ranibizumab for Age-Related Macular Degeneration

Systematic Review and Meta-analysis of Randomized Trials

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Background: We conducted a meta-analysis of randomized trials of ranibizumab for age-related macular degeneration (AMD) to elucidate systemic vascular risk.

Clinical Relevance: Although intravitreal vascular endothelial growth factor inhibitors are widely used to treat AMD, whether they produce systemic adverse effects remains uncertain.

Methods: We searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials through March 2014 to identify the randomized trials that compared systemic safety among different intensities of ranibizumab treatment for AMD. The outcome measures were the incidence of cerebrovascular accidents (CVAs), myocardial infarctions, nonocular hemorrhages, overall arterial thromboembolic events (ATEs), and all-cause mortality. We calculated the Peto odds ratio (OR) with 95% confidence interval for the comparisons between different intensities of regimens in terms of dose and retreatment frequency.

Results: Eleven trials comprising 6596 patients with AMD were included in the meta-analysis. A significant increase was observed in the following comparisons: 0.5 versus 0.3/0.0 mg for CVA (OR, 1.86; 95% CI, 1.05−3.29; $P = 0.03$), monthly versus pro re nata (PRN)/0.0 mg for CVA (OR, 1.89; 95% CI, 1.06−3.38; $P = 0.03$), and 0.3/0.5 versus 0.0 mg for nonocular hemorrhage (OR, 1.57; 95% CI, 1.01−2.44; $P = 0.04$). A nonsignificant increase was observed in the following comparisons: 0.5 versus 0.0 mg for CVA (OR, 2.27; 95% CI, 0.90−5.69; $P = 0.08$), monthly versus PRN for CVA (OR, 2.04; 95% CI, 0.94−4.45; $P = 0.07$), 0.5 versus 0.0 mg for nonocular hemorrhage (OR, 1.68; 95% CI, 0.98−2.88; $P = 0.06$), 0.3 versus 0.0 mg for nonocular hemorrhage (OR, 1.68; 95% CI, 0.95−2.98; $P = 0.07$), monthly versus PRN/0.0 mg for nonocular hemorrhage (OR, 1.54; 95% CI, 0.98−2.42; $P = 0.06$), monthly versus PRN for ATE (OR, 1.58; 95% CI, 0.96−2.61; $P = 0.07$), and monthly versus PRN/0.0 mg for ATE (OR, 1.42; 95% CI, 0.99−2.05; $P = 0.06$). Among the other analyses, no protective or harmful effects of ranibizumab were observed.

Conclusions: In ranibizumab treatment for patients with AMD, a possible relationship of more intensive treatment to more systemic vascular adverse events was identified, but no relationship with mortality was identified. *Ophthalmology 2014;121:2193-2203 © 2014 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

Age-related macular degeneration (AMD) is a leading cause of blindness worldwide.[1] After establishment of its efficacy to treat exudative AMD,[2,3] ranibizumab has been the most widely used[4] intravitreal vascular endothelial growth factor (VEGF) inhibitor that has received approval from the US Food and Drug Administration (FDA). Ranibizumab has also been the most intensively evaluated drug for its efficacy and safety through numerous randomized trials.

Despite the unquestionable effectiveness of VEGF inhibitors in restoring and improving the vision of patients with exudative AMD, as long as treatment frequency is maintained, the possible adverse effects on the systemic vasculature remain uncertain.[5−12] Some reports[6,7] have indicated an increased risk of cerebrovascular events with ranibizumab, whereas other postmarketing retrospective studies[9−11] have reported conflicting results.

The results of our previous meta-analysis of 3 randomized controlled trials indicated a significant increase in cerebrovascular accidents (CVAs) in response to ranibizumab treatment.[6] In contrast, in other meta-analysis reports, cerebrovascular and cardiovascular risks were not specifically evaluated.[13,14] In addition, non-AMD patients were included and different pharmacologic types of VEGF inhibitors were collectively discussed.[15] Since then, several other randomized trials investigating ranibizumab for AMD have been published; thus, we performed an updated meta-analysis to address the systemic risks associated with ranibizumab administration for patients with AMD.

Methods

We conducted a systematic review and meta-analysis based on a predefined protocol (Appendix 1; available at www.aaojournal.org).

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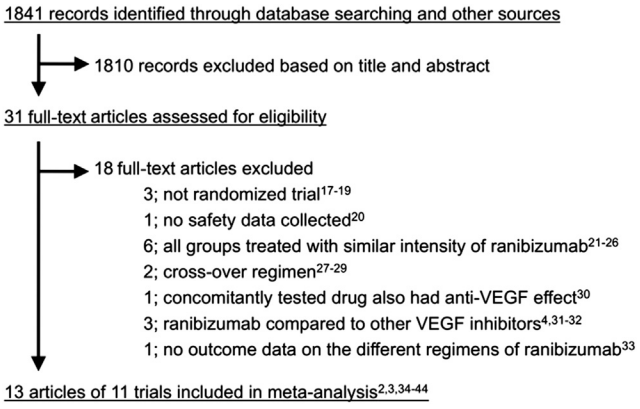

Figure 1. Selection of studies. VEGF = vascular endothelial growth factor.

Literature Search

We systematically searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases with no language restrictions from inception until March 2014. The key terms used for the systematic search were "macular degeneration," "choroidal neovascularization," and "ranibizumab," while restricting the search to randomized trials. The detailed search strategy is described in the protocol presented in Appendix 1 (available at: www.aaojournal.org). Two independent reviewers (T.U. and T.T.) performed the electronic searches. First, we assessed titles and abstracts and excluded reports that were apparently not randomized trials on ranibizumab use for AMD. After the initial screening, we retrieved full reports and assessed for eligibility. We also searched the reference lists of original studies and review articles identified by the electronic search for other potentially eligible articles.

Table 1. Characteristics of Included Studies

No. of Patients by Study	Dose/Injection	No. of Injections	Follow-up (mo)	Mean Age (yr)	Completion Rate (%)	Support by Manufacturers
MARINA 2006[2]						Yes
236	Sham	0	24	77	79.8	
238	0.3 mg	24	24	77	88.2	
239	0.5 mg	24	24	77	89.6	
FOCUS 2008[36,37]						Yes
56	PDT	0	24	73	85.2	
105	0.5 mg + PDT	24	24	75	85.2	
PIER 2008[38]						Yes
63	Sham	0	12	78	86	
59	0.3 mg	6	12	79	97	
61	0.5 mg	6	12	79	97	
ANCHOR 2006, 2009[3,35]						Yes
143	PDT	0	24	78	76.9	
137	0.3 mg	24	24	77	83.6	
140	0.5 mg	24	24	76	82.9	
SAILOR 2009[39]						Yes
1169	0.3 mg	4.6±1.7	12	79	81.4	
1209	0.5 mg	4.6±1.7	12	79	82.0	
CATT2011[41]						No
301	0.5 mg	12	12	79	93	
298	0.5 mg	6.9±3.0	12	78	93	
EXCITE 2011[40]						Yes
120	0.3 mg	6	12	75	88.3	
118	0.5 mg	6	12	76	80.5	
115	0.3 mg	12	12	75	89.6	
IVAN 2012[43]						No*
157	0.5 mg	12.2±1.6	12	78	98.2	
155	0.5 mg	7.5±2.9	12	78	98.2	
DENALI 2012[42]						Yes
210	0.5 mg + PDT	5.5	12	77	89.1	
111	0.5 mg	10.6	12	77	89.1	
EVEREST 2012[34]						Yes
21	PDT	0	6	62	96.7	
19	0.5 mg + PDT	3.9	6	64	96.7	
21	0.5 mg	5.2	6	69	96.7	
HARBOR 2013[44]						Yes
274	0.5 mg	11.3±1.8	12	79	94.5	
275	0.5 mg	7.7±2.7	12	79	94.5	
274	2.0 mg	11.2±2.1	12	79	94.5	
272	2.0 mg	6.9±2.4	12	78	94.5	

PDT = photodynamic therapy.
*The principal investigators and their hospital had financial relationships with the manufacturer.

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