Safety in Aflibercept versus Ranibizumab

Dear Editor:

Aflibercept seems to have equivalent effectiveness to ranibizumab, even though it requires less frequent injections.1 Although the effectiveness of vascular endothelial growth factor (VEGF) inhibitors for age-related macular degeneration (AMD) is unquestionable, there has been some concern for the systemic vascular safety, especially relating to cerebrovascular risk.2-4

VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) 1 and VIEW 2 were closely related randomized controlled trials conducted by a group of researchers according to the same study protocol.1 Second, although few events were listed as nonfatal stroke meeting APTC criteria. However, the number of the nonfatal strokes in the ranibizumab group should be 1, not 2, based on the record in the appendix of primary safety analysis sets where only one cerebrovascular accident (CVA) was recorded in the ranibizumab group, as well as the briefing document of the advisory committee in the FDA.gov,3 where the number of nonfatal strokes meeting APTC criteria was shown as 1, not 2. Although the difference may be small and does not change the insignificant difference between the 2 groups, considering that stroke is a major interest of adverse events, the integrity of the data could be important for the future evaluations.

Second, although few events were listed as nonfatal stroke meeting APTC criteria in the main text, more were listed in the appendix data. CVAs listed there comprise “cerebral infarction,” “CVA,” “lacunar infarction,” “subarachnoid hemorrhage,” “cerebral artery thrombosis,” “cerebral hemorrhage,” “cerebral infarction,” “ischemic cerebral infarction,” and "transient ischemic attack." Table 1 (available at http://aoajournal.org) shows the numbers of these total CVAs and nervous system disorders. Of the aflibercept- and ranibizumab-treated patients, 1.4% (25 of 1824) and 0.2% (1 of 595), respectively, experienced CVAs ($P = 0.014$ by chi-square test). In addition, the rates of total number of nervous system disorders were 0.5% (3 of 595) in the ranibizumab-treated patients and 2.1% (38 of 1824) in aflibercept-treated patients, respectively ($P = 0.0092$ by chi-square test).

Although the significant differences in the numbers of CVAs and nervous system disorders might be owing to the inclusion of milder cases such as transient ischemic attack as discussed in the briefing document from the advisory committee,2 we should not exclude information from future follow-up evaluations. Pharmacologic differences between aflibercept and ranibizumab, such as more continuous VEGF blockade and additional inhibition of placental growth factor, may be associated with the differences in the safety results.

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References

Author reply

Dear Editor:

Beaumont et al and Ueta raise concerns about the systemic safety of aflibercept for intravitreal injection, particularly regarding cerebrovascular risk and stroke, based on their analysis of safety data from the VIEW studies comparing aflibercept to ranibizumab.1 They acknowledge similar rates of serious adverse events (SAEs) overall between aflibercept and ranibizumab, as well as similar rates of myocardial infarction, stroke, and vascular death as confirmed by masked adjudication using the strict and well-accepted Antiplatelet Trialists’ Collaboration (APTC) criteria. However, they focus on numerical imbalances in certain other adverse events (AE) classifications to raise the question of whether aflibercept might be associated with a higher risk of stroke, while overlooking data that point to a higher incidence of cardiovascular events with ranibizumab.

While Beaumont et al point out that the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) drew attention to the issue of cerebrovascular events, they should have also pointed out that like the previous Food and Drug Administration (FDA) assessment, the CHMP concluded that “overall the safety profile of aflibercept appears to be similar to the already marketed comparator drug, ranibizumab.”2 Beaumont et al concede that their approach suffers from being a post-hoc subgroup analysis; it is well known that selectively singing out relatively small numbers of individual classes of AEs for post-hoc assessment, as these letters do, can lead to erroneous conclusions. Importantly, their assessments of statistical significance were neither prespecified nor corrected for multiplicity so that any claims made concerning statistical significance of any imbalances are invalid. In addition, since the overall SAEs between all treatments were well balanced, any numerical imbalances in the first year favoring ranibizumab had to be (and were) contrasted by other numerical imbalances favoring aflibercept (i.e., there were imbalances against ranibizumab regarding serious infections) (Table 1; available at http://aoajournal.org).3

Nevertheless, questions about the noted numerical imbalance favoring ranibizumab in the first year of the VIEW studies had previously prompted the sponsors to conduct further evaluations (the letters refer to imbalances within the overlapping “Nervous System Disorders” and non-adjudicated “arterial thromboembolic events” [ATEs] categories, which both include cerebrovascular events). These further evaluations were presented in detail to the regulatory authorities, contributing to their above-stated conclusions. If there were indeed a real risk associated with aflibercept, the noted

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