Cardiac Issues of Noncardiac Drugs: The Rising Story of Avastin in Age-Related Macular Degeneration

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Key Words

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Abstract

Emerging safety data, accompanied with recent demographic trends, point to the need for an in-depth review and consideration of potential consequences that might arise from continuing use of bevacizumab (Avastin®) to treat elderly patients presenting with wet age-related macular degeneration (AMD). Although it is expected that lower doses of Avastin used for intravitreal administration and an intact blood-retina barrier would reduce the systemic exposure of the drug, both animal and human studies suggest that this may not be the case. In addition, emerging real-world and clinical trial data continue to point toward compromises in both cardiovascular and cerebrovascular safety with Avastin. Thus, clinicians are urged to adopt the highest possible standard of care in the treatment of an already fragile AMD population. Furthermore, postmarketing surveillance and pharmacovigilance with intravitreal anti-VEGF inhibitors should remain a priority.

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Introduction

Over the past decade, several promising new therapies, directly [cerivastatin (Baycol®), rosiglitazone (Avandia®)] or indirectly [rofecoxib (Vioxx®)] related to car-

diac disease, have been withdrawn from the market due to an increase in the cardiovascular (CV) risk. As a result, the CV community is calling for an increase in pharmacovigilance and demanding careful assessment of the risk and benefit ratio of other agents with emerging safety signals. The most recent story involves the intravitreal use of antivascular endothelial growth factor (VEGF) therapies for the treatment of several ocular conditions, age-related macular degeneration (AMD) in particular.

It is well established that VEGF signaling plays a critical role in the homeostasis of the adult vascular system and that VEGF is essential for endothelial survival, and cardiovascular repair and regeneration [1]. Yet, the systemic safety of intravitreally administered anti-VEGF therapies has never been fully established. Furthermore, the off-label preparation and use of bevacizumab (Avastin®), an agent licensed for intravenous administration and treatment of various cancers, presents another serious concern.

This review summarizes the facts surrounding recent safety signals and questions associated with intravitreal off-label administration of Avastin for the treatment of wet AMD, the leading cause of blindness among the elderly in North America [2, 3]. The use of an off-label drug to treat a condition for which another agent, in this case ranibizumab (Lucentis), has been approved creates numerous medical and health policy-related controversies, especially in lieu of accumulating evidence pointing to compromised ocular and systemic safety, cardiovascular (CV) in particular, associated with the intravitreal ad-

Fig. 1. Adjusted HRs of adverse events at 1 year in patients receiving Lucentis compared with Avastin as first-line therapy [11]. MI = Myocardial infarction.

ministration of Avastin. Emerging safety data, accompanied with recent demographic trends, point to the need for an in-depth review and consideration of potential consequences that might arise from continuing use of Avastin to treat elderly patients presenting with wet AMD.

Emerging Safety Signals Associated with Intravitreal Avastin

The observations that intravenous administration of Avastin and systemic inhibition of VEGF in cancer patients carries significant CV risks – including hypertension, arterial thrombosis, and cardiomyopathy [4] – led to questions in regard to systemic effects of intravitreal administration of anti-VEGF therapies. Furthermore, as the SAILOR trial indicated, an increased risk of stroke with Lucentis®, especially in patients with a history of prior stroke and arrhythmia [5], one should also question whether Avastin would pose a similar, if not higher, risk. Although it is expected that lower doses of Avastin used for intravitreal administration and an intact blood-retina barrier would reduce the systemic absorption of the drug, a study in rabbits demonstrated the presence of the drug in serum up to 7 days following intravitreal injection [6]. Recent studies by Barros-Pereira et al. [7] and Carneiro et al. [8] revealed significant reductions in systemic VEGF plasma levels during the 28-day period after intravitreal administration of Avastin in patients with AMD. Intravitreal Lucentis, however, has not been associated with a

similar prolonged and significant reduction in systemic VEGF levels.

Interim analysis of the Inhibit VEGF in Age-Related Choroidal Neovascularisation (IVAN) trial confirmed the results from previous pharmacokinetic studies [9]. Median serum VEGF concentrations at 1 year (151 pg/ml for Lucentis and 83 pg/ml for Avastin) were significantly lower with Avastin (geometric mean ratio, 0.47; 95% confidence interval, CI, 0.41–0.54; $p < 0.001$). From this, the IVAN investigators speculated that the consequences of the differential suppression of circulating VEGF might only become apparent after a longer follow-up time.

Until recently, evidence pointing to the effects of intravitreally administered Avastin on systemic VEGF blockade and CV safety was scarce. A small population-based study, by Rasier et al. [10], demonstrated that in patients with a history of treated hypertension, Avastin was associated with an 11.8/6.2-mm Hg increase in blood pressure 3 weeks after intravitreal injection ($p < 0.001$), and remained significantly elevated above baseline at 6 weeks of follow-up. Significant and sustained elevation over baseline was also seen in normotensive patients although to a lesser degree (approx. 5/4 mm Hg elevation, $p < 0.001$) [10]. Several studies published recently have further raised concerns within the ophthalmology community.

First, a retrospective analysis of 146,942 Medicare case records noted a significantly lower risk of stroke by 19% in patients treated with Lucentis compared with Avastin (hazard ratio, HR, 0.81; 99% CI, 0.68–0.98) [11] (fig. 1). In addition, a secondary analysis that included only patients treated with either Avastin ($n = 21,815$) or Lucentis ($n = 19,026$) as first-line therapy also reported a 22% lower stroke rate with Lucentis (HR, 0.78; 95% CI, 0.64–0.96) and a 14% lower mortality rate as compared to patients treated with Avastin (HR, 0.86; 95% CI, 0.75–0.98).

Further analysis by Gower et al. [12] that included 77,886 patients (46% Lucentis) indicated a 57% higher risk of hemorrhagic stroke (HR, 1.57; 99% CI, 1.04–2.37) and an 11% higher risk in all-cause mortality (HR, 1.11; 99% CI, 1.01–1.23) in individuals treated with Avastin compared to Lucentis.

Finally, a smaller retrospective analysis of 378 patients treated with either Lucentis or Avastin for at least 1 year also revealed a significantly higher incidence of atherothrombotic events in patients treated with Avastin compared to those receiving Lucentis: 12.4% (12/97) versus 1.4% (3/219); $p < 0.0001$ [13] (table 1).

Table 1. Ratio of atherothrombotic events (ATEs) in bevacizumab versus ranibizumab groups

	ATE yes	ATE no	Sum
Avastin	12	85	97
Lucentis	3	216	219
Sum	15	301	316

Fisher's exact test: $p < 0.0001$. Odds ratio = 10.16; 95% CI = 2.80–36.93.

Impact of the CATT Trial on Clinical Care

The highly anticipated Comparison of Age-Related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial (CATT) left the ophthalmology community with more questions than answers [14, 15]. This noninferiority study compared monthly treatment of either Avastin or Lucentis with as-needed regimens and demonstrated equivalent 1-year visual acuity outcomes (primary end point) with monthly Lucentis or Avastin. However, while 1-year results with as-needed (or pro re nata, PRN) Lucentis combined with monthly assessments appear to be as effective as monthly treatments, results with as-needed Avastin were inconclusive. Surprisingly, the number of treatments required in the Avastin as-needed arm was significantly higher than in the Lucentis arm (7.7 vs. 6.9 injections; $p = 0.003$). This is contrary to the commonly held belief that, due to longer half-life, treatment with Avastin lasts longer. After 2 years of treatment, the mean gain in visual acuity was, however, significantly greater for patients treated monthly compared to patients treated PRN (difference, -2.4 letters; 95% CI, -4.8 to -0.1 letters; $p = 0.046$) [15].

Although more patients treated with Avastin experience serious adverse events (SAEs), mostly hospitalization, these and other safety data must be interpreted with caution as the CATT trial was not sufficiently powered to conclusively establish differences in AEs between the two compounds.

The higher SAE rates reported in year 1 for Avastin-treated patients were also noted during the second year. Compared to Lucentis, Avastin was associated with a higher proportion of patients having 1 or more systemic SAEs (39.9 vs. 31.7%; $p = 0.009$) [15]. As by protocol, 50% of each cohort receiving monthly injections were crossed over to a PRN treatment regimen after 1 year, one would expect the SAEs to proportionally decrease as well. However, this was not the case.

Potential Impact of Differences in the Molecular Structure

Both Avastin and Lucentis come from a mouse anti-VEGF monoclonal antibody [16]. However, different Fab fragments were used as precursors. In the case of Avastin, 2 Fab-12s were placed on a crystallizable fragment (Fc) fragment and then produced in a Chinese hamster ovary mammalian cell line. This led to glycosylation of protein and a longer half-life within the systemic circulation, allowing the drug to last longer in order to treat cancer. The Fc fragment of Avastin also facilitates transport of the molecule from the eye into the circulation, creating a theoretically higher risk of systemic AEs compared to Lucentis [17].

A larger protein load, a result of the additional Fc fragment, might also be a cause of clusters of sterile endophthalmitis reported in Canada [18] and worldwide [19]. Gower et al. [12] also reported an 80% higher risk of endophthalmitis with Avastin compared to Lucentis (HR, 1.8%; 99% CI, 1.2–2.8). The Fc fragment of Avastin promotes elimination from the eye back into the circulation, which might induce an immune-system response despite very low concentrations of the drug. In support of this is the observation that the likelihood of experiencing an adverse event increases with the number of injections the patient had previously received (odds ratio, 2.29; $p = 0.0157$) [18]. The 'sensitized' patients had a higher relative risk of developing severe inflammation/endophthalmitis. As a result of their concern over the risk of sterile endophthalmitis, in November 2008, Hoffmann-La Roche and Health Canada issued a letter notifying physicians of possible outbreaks of eye inflammation, endophthalmitis, and a form of toxic sterile vitritis, following Avastin injection [20]. Health Canada also requested the addition of a 'serious warning and precaution' to the Avastin product monograph indicating that the agent has not been authorized for intravitreal use and that local and systemic adverse events have been reported in the post-marketing setting with unauthorized intravitreal use of the drug [21].

Packaging Issues and Off-Label Administration

Avastin is packaged in single-use, sterile, preservative-free vials for intravenous use in the oncology settings. The practice of repackaging single-use Avastin vials into syringes carries a risk of contamination. In fact, clusters of cases of bacterial infection and eye inflammation result-

ing in blindness or near blindness have recently been reported in 3 locations in the USA in patients treated with repackaged intravitreal Avastin [22]. This resulted in another letter issued by Hoffmann-La Roche and Health Canada on December 7, 2011, reminding healthcare professionals that injecting Avastin into the eye is not authorized by Health Canada and may carry serious consequences [23].

Similarly, due to some individual cases and clusters of ocular SAEs that resulted in various degrees of visual loss (including permanent blindness), the committee for Medicinal Products for Human Use of the European Medicines Agency updated the label for Avastin with warnings of ocular and systemic AEs events following unauthorized intravitreal use [24]. Following this safety update to the Avastin label, the Science and Technology Commission of the Italian Medicines Agency AIFA ordered the removal of intravitreally used Avastin from the reimbursement list [25].

Underreporting of AEs: Serious Concern with Off-Label Use

The concern over AEs when a drug is used off-label is often enhanced because the events might not always be reported accurately or to the appropriate authorities. Although many serious drug toxicities (Vioxx and Avandia being the latest examples) are detected by postmarketing surveillance studies, tracking such events is difficult when the drug is used off label. In addition, patients with AMD often present with multiple conditions that might contribute to AEs regardless of the AMD-related treatment. Taking this into consideration, retina specialists administering anti-VEGF therapies need to be extra vigilant and take into consideration the full patient profile. They also need to ensure that appropriate follow-up is in place.

Population Trends: From Increased CV Risks to Aging Population

Numerous studies support the notion that AMD and CV disease share the same risk factors [26–28]. Patients being treated for AMD are, in general, in an age group with a higher risk of CV and cerebrovascular comorbidities. These patients have an 18% higher risk of stroke, a 36% higher risk of hypertension, a 40% higher risk of having elevated cholesterol [29], and a 26% higher rate of myocardial infarction [30] compared with control pa-

tients who did not have AMD. Furthermore, recent population trends in Canada show a considerable increase in CV risk factors over a 10-year period, including a near doubling of the prevalence of hypertension [31]. The burden of CV risk factors is higher in the eastern Maritime provinces and among individuals with lower socioeconomic status. This suggests that, from a socioeconomic standpoint, patients who are more likely to be candidates for Avastin are also more likely to be at risk of experiencing CV events.

Conclusion

The observed increase in CV risk factors within our aging population is of serious concern to all physicians. As seen from the data, this concern now extends to the exacerbated risk for CV events seen in AMD patients receiving Avastin versus Lucentis, and thus the need for clinicians to adopt the highest possible standard of care in the treatment of AMD.

In addition to effectively treating AMD, an important goal must also be to reduce and potentially avoid therapy-related CV events that pose a significant burden to patients, their families, the healthcare system, and society.

Furthermore, postmarketing surveillance studies measuring pharmacovigilance with intravitreal anti-VEGF inhibitors, both Avastin and Lucentis, should be made mandatory.

At this time, as a precaution, and to ensure optimal care, we strongly recommend that retina specialists, as well as general ophthalmologists, avoid the use of Avastin in AMD patients with a history of stroke, hypertension, established CV disease or those with a high Framingham risk score for CV disease.

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