Department of Ophthalmology and Vision Sciences

Ophthalmology

FACULTY OF MEDICINE
University of Toronto

Scientific Update™

A REPORT BY THE DEPARTMENT OF OPHTHALMOLOGY AND VISION SCIENCES, FACULTY OF MEDICINE, UNIVERSITY OF TORONTO

Severe Intraocular Inflammation/Endophthalmitis Following Off-label Treatment with Intravitreal Bevacizumab

Reported and discussed by:
ALAN R. BERGER, BSC, MD, FRCSC, and
SANJAY SHARMA MD, MSC (EPID), MBA

Canadians with choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) have been receiving treatment for 3 years with the vascular endothelial growth factor (VEGF) inhibitors, ranibizumab and bevacizumab. While ranibizumab was developed specifically for intraocular use in the treatment of CNV, bevacizumab was developed as a treatment for metastatic colorectal cancer. Bevacizumab was not developed for ocular use, and has not been approved anywhere in the world by government health regulatory bodies for intravitreal use in the treatment of ocular CNV. While used by many retinal specialists for the treatment of neovascular AMD, intravitreal injection of bevacizumab is an off-label use of this agent; it is therefore incumbent on the clinician to discuss with patients the details concerning the risks, clinical experience, alternatives, and potential benefits of this drug. Patients should be informed that there have been no large-scale prospective, randomized safety or efficacy trials with this agent, unlike the approved agent, ranibizumab.

In 2006, 2 randomized, prospective, multicentre clinical trials were published – MARINA[1] and ANCHOR[2] – documenting the efficacy and safety of ranibizumab for CNV secondary to AMD. These studies paved the way for the approval of ranibizumab for neovascular AMD in Canada. While ranibizumab was undergoing phase III testing, Rosenfeld and colleagues at the Bascom Palmer Eye Institute, University of Miami, initiated a study treating AMD patients with bevacizumab,[3,4] a drug that is related to ranibizumab, but one that was approved for use in patients with metastatic colorectal cancer. Both of these anti-VEGF drugs are now extensively used in Canada for the treatment of wet AMD and other retinovascular diseases, but bevacizumab has not been approved by Health Canada for intraocular use for any indications.[5]

Concern over adverse events

Although ranibizumab and bevacizumab appear to produce comparable outcomes in patients who are treated for AMD, the evidence for the safety of these 2 drugs is different. Ranibizumab has been studied extensively in large prospective, randomized, controlled trials (RCTs) with >7500 patients, as well as in meta-analyses that specifically examined safety issues. These studies of ranibizumab, which will be discussed in more detail, have found that the rates of both ocular and systemic adverse events are very low. To date, no well-designed, large-cohort, prospective, level 1 RCTs have examined the efficacy and safety of bevacizumab intravitreal injections, nor have large prospective, randomized safety studies examined bevacizumab for ophthalmic use. Three retrospective chart reviews,[6-8] involving more than 21 840 patients, have placed the incidence of endophthalmitis following intravitreal injections with VEGF inhibitors at ≤2%. One of these reviews involved both ranibizumab and bevacizumab, and 2 involved only bevacizumab.

The concern over adverse events when a drug is used off-label is heightened because when such events occur, they

Department of Ophthalmology and Vision Sciences, Faculty of Medicine, University of Toronto, 60 Murray St. Suite 1-003 Toronto, ON M5G 1X5

may not always be reported accurately or to the appropriate authorities. Many serious drug toxicities are detected only through postmarketing surveillance, but the means to track such events do not exist when a drug is used off-label. As a result, when drugs are used in an off-label fashion, adverse events may be significantly underreported.

Given this situation, the ophthalmologist cannot rely solely on published clinical trials to determine the frequency of adverse events from the use of off-label products such as bevacizumab. Most interventional ophthalmic trials are powered to detect changes in efficacy. It is important to remember that trials are typically powered to detect clinically relevant differences; the larger the clinical relevance being sought, the smaller the sample size. Because differential adverse event rates usually differ by orders of magnitude when compared with safety differences, most efficacy trials are underpowered to detect clinically relevant differences in safety.

The Canadian experience

Recently, a number of retinal subspecialty groups in Canada and other countries have reported case clusters of bevacizumab-associated ocular adverse events, including acute anterior-segment inflammation with or without hypopyon, vitreous inflammation, or raised intraocular pressure. Many of these cases were aggressively treated as possible cases of infectious endophthalmitis.

At the recent meeting of the Canadian Ophthalmological Society, held in Toronto, June 20-23, 2009, data were presented on 3 outbreaks of serious ocular adverse events following intravitreal bevacizumab use.

Michael Fielden, MD (Alberta Children's Hospital, Calgary, Alberta),[9] presented data on a cluster of acute ocular inflammation cases following intravitreal bevacizumab injections. At one retinal practice in Calgary, 4 physicians performed these injections, and 27 eyes of 23 patients developed uveitis after a mean of 5.8 injections. Onset of symptoms occurred, on average, 1.8 days after the injection: 23 eyes had CNV membranes, 3 had diabetic macular edema, and 1 had macular edema secondary to central retinal vein occlusion. Symptoms included a decrease in visual acuity, floaters, photophobia, and mild-to-moderate eye pain. At the initial presentation of symptoms, visual acuity was decreased in 22 of the 27 eyes. The mean follow-up time of this patient group was 112 days, during which the patients were treated with topical corticosteroids and antibiotic therapy, such that 21 of the 27 eyes regained equal or better than baseline visual acuity.

Riley Hall (fourth year medical student, University of Saskatchewan, Saskatoon)[10] presented data from a 30-month retrospective chart review examining adverse events among 171 patients who had received a total of 1461 injections of intravitreal bevacizumab. All of the patients were treated at a single retinal practice in Calgary. There were 40 ocular adverse events found in 32 patients, for a 2.69% event rate. These events occurred after a mean of 4.8 injections. Patients were undergoing treatment for CNV secondary to AMD, as well as other conditions including branch and central retinal-vein occlusion, and diabetic eye disease. The most common adverse events were eye pain, transient increases in intraocular pressure, and corneal abrasions (12, 7, and 6 patients, respectively). There were no recorded cases of endophthalmitis, lens injuries, or retinal detachments. The review also found 9 systemic adverse events, including 1 transient ischemic attack, 1 stroke, and 3 acute myocardial infarctions. Mr. Hall concluded that these event rates were similar to reports previously found in the literature, and that the systemic events could not be definitively attributed to bevacizumab use, since all of these patients had prior medical histories of cardio- and cerebrovascular events and/or significant risk factors for cardiovascular disease.

In Kingston, where 2 retinal specialists – 1 of whom is an author of this paper (SS) – deliver the retinal care for Southeastern Ontario, over a dozen cases of inflammation were noted following intravitreal injection with bevacizumab. While no incident cases were noted in the first 1000 cases in which bevacizumab was injected, the incidence of severe

Table 1: Cases of bevacizumab-associated acute ocular inflammation, as of February 22, 2009

City	Cases
Vancouver	22
Vancouver	5
Victoria	8
Calgary	27
Regina	5
Toronto	6
Kingston	14
Montreal	4
Montreal	3 (different lot #)
Québec	6
Sherbrooke	3
Trois-Rivières	7
Halifax	6
Halifax	1
TOTAL	117

Holland S (unpublished data). Presented at Angiogenesis, Exudation, and Degeneration 2009. Key Biscayne, FL, February 21, 2009.

inflammatory reactions rose to a rate approximating 1 in every 50 injections over a 6-month period from August 2007 to January 2008. Most cases presented within 24-48 hours following injection with significant ocular pain and redness following injection; many subjectively also noted significant floaters. Cases involved hypopyon, dense vitritis, and intractable glaucoma, and some cases required anterior chamber tap and injection with intravitreal antibiotics, vitrectomy and filtration surgery. A local *ad hoc* task force was implemented to investigate process changes to determine the source for the outbreak over this 4-month period. Only after initiating the policy of topical post-injection steroids did the incidence fall. The approval of ranibizumab coincided with the tail end of the bevacizumab inflammatory outbreak (manuscript in preparation).

Simon Holland, MD (University of British Columbia and BC Centre for Disease Control, Vancouver),[11] presented findings from a national task force that examined a series of inflammation outbreaks following intravitreal bevacizumab injections (Table 1). Dr. Holland reported on an outbreak of 21 cases of acute ocular inflammation that occurred at the University of British Columbia over a 9-day period in October 2008. These patients presented with moderate to severe inflammation, blurred vision, photophobia, and the presence of floaters. Symptoms occurred 1-3 days after the bevacizumab injection, but only 3 of the 21 patients reported experiencing eye pain. Retinal specialists across Canada were not immediately informed of this outbreak.

On October 31, 2008, within 2 weeks of the unreported cluster of cases in BC, one of the authors of this paper (ARB) noted 6 cases of severe inflammatory reactions shortly after patients received intravitreal bevacizumab injections at his retinal practice in Toronto. Five patients complained specifically of eye pain worse than they had ever experienced from prior injections of bevacizumab, 4 patients were found to have moderate anterior-chamber reaction, and 3 had moderately elevated intraocular pressure. All of the patients responded positively to intensive corticosteroid therapy, but they all had continuing symptoms of floaters or blurred vision for periods ranging from 3 to 8 weeks. None of the patients were thought to have endophthalmitis and, as a result, none of these patients required intravitreal intervention with either pars plana vitrectomy, vitreous tap, or injections of intravitreal antibiotics. All patients in the group recovered acuity back to their baseline level.

These cases of adverse drug events related to intravitreal bevacizumab prompted formal reports to be sent by Dr. Holland and the author (ARB) to Health Canada, Hoffmann-La Roche Canada Limited (distributor of bevacizumab), and Genentech Inc. Dr. Holland, head of the Canadian Ophthalmological Society (COS) task force on toxic anterior segment syndrome (TASS; characterized by sterile inflammation) and endophthalmitis, issued a "member alert" in November 2008, notifying physicians of possible outbreaks of endophthalmitis following bevacizumab injections. The COS alert noted that patients in all of these cases were treated with bevacizumab from the same manufacturer's lot and batch number, and recommended that further injections from this lot number and batch be suspended.

A letter to physicians posted on the Health Canada website[12] in December 2008 noted that as of that date, 25 cases of sterile endophthalmitis had been reported following bevacizumab injections. Health Canada's website has not published any further data concerning adverse events associated with bevacizumab use since the December 2008 letter to physicians.

The COS has established a TASS/Infectious Disease (ID) Task Force Hotline to follow this important emerging issue for Canadians. Dr. Holland indicated in his presentation that, as of April 2009, 105 cases of inflammation and/or sterile endophthalmitis from 13 centres across Canada had been reported to his office.[11]

Potential causes for inflammation/ endophthalmitis following bevacizumab use

Following a thorough investigation of the Canadian outbreak by the COS, Hoffmann-La Roche, and Health Canada, one possible factor suggested for the outbreak of endophthalmitis was contamination of the individual bevacizumab vials by excess residues of silicone oil in the lot/batch sample.[11] Laboratory analyses including mass spectrometry, gas chromatography, and testing for both endotoxins and benzalkonium chloride (BAK) were conducted. Slightly elevated levels of polydimethylsiloxane (PDMS; a specific type of silicone oil) were detected in the samples tested when compared with a control sample. Furthermore, 2 specific residues of PDMS, m/z248 and m/z249, were found in the samples. In the case of m/z248, the concentration was twice that seen in the control samples.

Another potential cause for severe intraocular inflammation is the presence of "excess particulates" in the formulated drug. Bevacizumab was developed and is produced as an antineoplastic agent for intravenous use, with doses in the range of 5.0-10.0 mg/kg of body weight recommended for systemic cancer therapy. Patients receiving off-label bevacizumab for the treatment of AMD typically receive intravitreal doses of 1.25-1.5 mg. The presence of excess particulate matter may not be an issue when a cancer patient is receiving a large dose of 500 mg diluted into their entire blood volume, but it could be problematic when even small amounts are injected into the vitreous cavity. This fact would not explain why only isolated clusters of severe intraocular inflammation have occurred, however, since it is expected that all vials would have similar levels of particulate matter.

Most bevacizumab used for intravitreal injections is prepared in compounding pharmacies under strict conditions of sterility and accuracy. Most vials are subdivided into aliquots of 0.1-0.2 cc to be used for the actual intravitreal injections. Such vial splitting, or multidosing, is not authorized, nor is it condoned by the manufacturer.[13] Bevacizumab that is manufactured for oncology applications is packaged in containers of 100 mg each. When these containers are broken down into smaller doses for ocular use, either in a pharmacy or in a clinical setting, there is a risk of microbial or viral contamination due to improper or inadequate handling procedures. It is important to note that any single 500-mg bevacizumab bottle that might be contaminated or tampered with prior to the subdivision process could potentially cause severe ocular inflammation or infection in upwards of 28 separate eyes.

In contrast, ranibizumab is delivered in single-use vials containing 0.23 mL, without intermediary handling by any compounding pharmacy. Since these vials are not broken down into smaller doses, the risk of contamination is minimized, and the risk of affects on multiple eyes by the same "contaminant" is minimized or eliminated. The American Society of Hospital Pharmacists[14] has advised that numerous factors, including sterility of the pharmacy setting, toxicity, pH and buffering, the use of preservatives, and the solubility of the drug must be considered when preparing ophthalmic products, particularly those for intravitreal use.

An important issue in the use of bevacizumab as an intravitreal treatment for AMD is also that, while normal intravitreal pH should be in the range of 6.5-8.5, the pH of bevacizumab in solution is below this threshold, at 6.2.[15] Once again, this is not likely to have been a factor in the clusters of inflammation/endophthalmitis cases reported in Canada.

Another potential explanation for excessive inflammation following intravitreal bevacizumab may be its larger protein load, a result of the additional Fc fragment compared with ranibizumab.[16] As only the molecular fragment with the VEGF-binding receptor, ranibizumab theoretically passes more readily through the retina and may work faster than the full-sized bevacizumab molecules. The Fc component of bevacizumab promotes elimination from the eye back to the circulation, which may lead to accumulation in platelets, increasing the agent's systemic half-life. This may induce an immunogenic response, despite the very low concentrations of the drug found systemically and possibly offer a partial explanation. Patients who had previously received intravitreal bevacizumab were "sensitized" and had a higher relative risk of developing the severe inflammation/endophthalmitis in the cases reported by Dr. Holland.

According to Dr. Holland, the specific causes of the outbreaks in Canada have not been positively identified, but variations in drug preparation, surgical procedures, and location of the retinal practices were not considered risk factors. Dr. Holland stated that all of the affected patients received bevacizumab from the same manufacturer's lot/batch number (odds ratio [OR] 25; $P<0.0001$), which likely indicates a specific contaminant/abnormality of that specific lot and batch. The likelihood of experiencing an adverse event also increased with the number of injections the patient had previously received (OR 2.29; $P=0.0157$). Age and sex of the patient were not predictive of these adverse events.

Safety issues not limited to Canada

Cases of endophthalmitis and/or inflammation among patients treated with bevacizumab have been reported in the United States, Australia, Britain, and the European Union. This has led regulatory authorities and professional associations in some European countries to issue guidelines informing doctors of the risks involved with off-label bevacizumab use. In other countries, restrictions have been placed on the off-label use of the drug.

An Australian study[17] reported 14 cases of ocular inflammation in a cohort of patients who received a total of 1278 injections of intravitreal bevacizumab. These were elderly patients, mean age 83.7 years, who had previously received an average of 2.7 injections (range 1-6). Most of the patients reported a painless but substantial reduction in vision occurring anywhere within 24 hours to 6 days following the injection. There were signs of inflammation present in both the anterior and posterior segments. Following intensive treatment with topical steroids, vision returned to baseline within 25 days for most of these patients.

A large, open-label, uncontrolled, multicentre, interventional case series conducted in 7 Latin American countries[18] reported 7 cases of bacterial endophthalmitis (0.16%), 7 cases of tractional retinal detachment (0.16%), and 4 cases of uveitis (0.09%) among 1173 patients who received a total of 4303 injections of intravitreal bevacizumab. Patients with uveitis were managed with intravitreal corticosteroids, while patients with endophthalmitis were managed with pars plans vitrectomy (PPV; n=5) or PPV with intravitreal corticosteroids (n=2). Six of the 7 eyes with endophthalmitis experienced significant, permanent vision loss. It should be stated that in this review, the majority of patients (84%) received 2.5-mg doses of bevacizumab, which is generally double the dosage most commonly prescribed worldwide.

As a result of their concern over the risk of adverse events, the Royal College of Ophthalmologists (RCO) in the United Kingdom (UK) has categorically recommended against the routine use of intravitreal bevacizumab for the treatment of wet AMD when another anti-VEGF drug, ranibizumab, for which a formal indication has been given, is available. The RCO, in issuing its 2009 guidelines,[19] noted

that medium- and long-term safety data concerning bevacizumab are unknown, since no long-term randomized studies have been conducted and the side effects of intravitreal bevacizumab remain undocumented. The RCO recommendations stated that the dose frequency for bevacizumab use is also unknown. They note that it is important to inform patients that bevacizumab is not indicated for AMD, asserting: "Bevacizumab is unlicensed and its 'off-label' status should be clearly stated prior to its use in patients. There are no long-term results on safety and effectiveness of intravitreal bevacizumab."[19] Further, if intravitreal bevacizumab is to be used, the clinician is exhorted to maintain a very detailed record of all data relevant to the use of this drug with every patient. They state that the clinician must also discuss alternative treatments in detail with the patient, and the appropriate informed consent must be obtained according to preferred practice guidelines. In a separate communication,[20] the RCO reminded clinicians in Britain that if an adverse event occurs as a result of using any drug off-label, the responsibility for any consequences would rest with the physician alone, noting: "Responsibility for prescribing drugs outside the terms of the product licence remains that of the prescriber i.e. the clinician."

The UK General Medical Council states that a physician prescribing a medication off-label should "(b)e satisfied that it would better serve the patient's needs than an appropriately licensed alternative" and "(b)e satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy."[21]

In Italy, the federal licensing authorities have rescinded prior directives that would cover the cost of bevacizumab in the treatment of wet AMD. Interestingly, Italian patients who have been treated with off-label bevacizumab will be disqualified from healthcare coverage in the event that their macular degeneration continues to progress, and treatment with any other approved anti-VEGF drug becomes necessary.

Medical-legal issues

The issue of using an off-label drug to treat a condition, for which another drug has been approved, remains controversial for both medical and legal reasons. Echoing the warning from Britain's RCO about the legal implications of off-label drug use, the courts in Germany have recently ruled that when a drug is used off-label, the physician, not the manufacturer, bears the legal responsibility.

In Canada, the issue of who may be liable in a case where the patient is injured through the use of an off-label product has not been decided in the courts. Personal communication with the Canadian Medical Protective Association has indicated that the association would defend any practitioner using a therapy, even if it is an off-label drug, if it is deemed to be a reasonable standard of care within their community. Whether bevacizumab represents "a reasonable standard of care for the treatment of wet AMD in all provinces of Canada" remains a debatable point.

Differences between drugs

Although bevacizumab and ranibizumab are both VEGF inhibitors and are derived from the same molecule, they are not identical drugs. Bevacizumab is a full-length immunoglobulin antibody with a molecular weight of 149 kD. Ranibizumab is the fragment antigen-binding (Fab) portion of the molecule, comprising only the active binding site of bevacizumab. It is approximately one-third the molecular weight of bevacizumab (48 kD). Due to their differences in molecular weights, *in vitro* studies with ranibizumab have demonstrated that it penetrates the retinal and internal limiting membrane more readily than bevacizumab and it is cleared from the body more rapidly than the larger molecule.[22-24] Ranibizumab also has an approximately 100 times greater affinity for VEGF, which translates into a 30- to 100-fold increased potency in bioassays that measured human VEGF-induced endothelial cell mitogenesis, and a 5-20 times greater potency than bevacizumab.[25] Recent evidence also indicates that bevacizumab accumulates in the retinal pigment epithelial cells.[26] Although not yet proven, there exists the theoretical risk that the extended serum half-life of bevacizumab versus ranibizumab may induce more patient risk for ocular and systemic adverse events. It is believed that a certain level of VEGF is needed in the body to facilitate wound healing and other physiological processes. Therefore, while VEGF inhibition is desirable in the treatment of CNV secondary to AMD, it may not be ideal to eradicate VEGF completely from the serum. VEGF depletion may be associated with the higher risk of stroke and myocardial infarction, and could present additional risks for patients with diabetes.[27]

Safety concerns

Bevacizumab compared with ranibizumab

As previously discussed, bevacizumab has not been subjected to any large-scale clinical trials to evaluate its safety. By comparison, ranibizumab has revealed a relatively low rate of ocular adverse events in a number of large trials. The HORIZON trial[28] followed 768 patients who had been previously enrolled in the MARINA,[1] ANCHOR,[2] and FOCUS[29] studies and treated with ranibizumab. The trial found only 1 case (0.2%) of vitreous hemorrhage, and no cases of either endophthalmitis or uveitis over 1 year of ranibizumab use. Serious and nonserious intraocular events, including uveitis, occurred in approximately 11.4% of patients in the first year of the FOCUS study. Many of these cases of inflammation were considered due to the lyophilized formulation of the

drug, which required reconstitution to a liquid before an injection was given. No serious intraocular events were reported once the switch was made to the liquid formulation. No systemic adverse events were seen that had not been anticipated from the original Phase III studies. The gains in visual acuity that these patients experienced in the Phase III trials were maintained throughout the first year of the HORIZON analysis. Among a subgroup of 110 patients, who had either received ranibizumab plus verteporfin photodynamic therapy (PDT) at some point during the original trial (n=64) or were receiving ranibizumab for the first time (n=46), 1 case of ocular inflammation (iritis) was recorded, and that patient was in the cohort previously treated with verteporfin PDT.

Hypertension is a recognized complication of bevacizumab as an antineoplastic agent;[30-32] however, its effect on blood pressure (BP) levels is less clear when administered intravitreally. Rasier et al[33] found that intravitreal bevacizumab was associated with significant increases in systolic and diastolic blood pressure (BP), both in normotensive and hypertensive subjects (N=82). In the group with established hypertension, systolic BP measurements were consistently elevated at 1, 3, and 6 weeks of treatment ($P=0.001$, $P<0.001$, and $P=0.003$, respectively) and diastolic BP levels were higher at 3 and 6 weeks ($P<0.001$ and $P=0.016$, respectively). In normotensive subjects, mean systolic and diastolic BP were significantly higher only at 3 weeks ($P=0.004$ and $P<0.001$, respectively). Conversely, in a retrospective review of intravitreal bevacizumab in 707 patients (1300 injections), Shima et al[34] identified only 2 elevations of systolic BP. As well, Gregori et al[35] detected a slight mean decrease in BP levels (-3/-3 mm Hg), with a range of -45 mm Hg to +43 mm Hg, in 36 patients undergoing intravitreal bevacizumab therapy for branch and hemiretinal vein occlusion.

Pooled safety data for ranibizumab reveal no significant changes in BP compared with placebo.[36]

SAILOR study

The largest analysis of safety data with ranibizumab is the Safety Assessment of Intravitreal Lucentis for Age-Related Macular Degeneration (SAILOR)[37] study. This 1-year, Phase IIIb trial involved 2378 patients who were treated with 0.3 mg or 0.5 mg of intravitreal ranibizumab in 3 initial doses at 1-month intervals, followed by quarterly doses (ie, every 3 months) according to prespecified criteria. The cohorts included patients who were treatment-naïve, as well as patients who had received previous treatments for their disease. Ocular adverse events, including presumed endophthalmitis and vitreous hemorrhage, did not exceed 0.4% and 0.9%, respectively, in any arm of the study (Table 2). Although there were more cases of death from any cause numerically, including vascular death, myocardial infarction, and stroke among patients who received the 0.5-mg dose of ranibizumab versus the 0.3-mg dose, these differences were not statistically significant. More cases of ischemic stroke were seen among patients who had had a prior stroke, regardless of the treatment received, but again, the between-group differences were not significant.

Table 2: SAILOR: key serious ocular adverse events[18]

	Cohort 1		Cohort 2
Event,% (n)	**0.3 mg (n=1169)**	**0.5 mg (n=1209)**	**0.5 mg (n=1922)**
Presumed endophthalmitis	0.2 (2)	0.4 (5)	0.1 (1)
Uveitis	0	0.1 (1)	0
Retinal detachment	0.1 (1)	0	0.1 (1)
Retinal tear	0	0.1 (1)	0
Retinal hemorrhage	0.9 (11)	0.9 (11)	0.3 (6)
Detachment of retinal pigment epithelium	0	0.2 (2)	0.1 (2)
Vitreous hemorrhage	0.3 (4)	0.1 (1)	0.2 (3)
Cataract	0.1 (1)	0.1 (1)	0.1 (1)

Under-reporting

Even important clinical trials can underestimate the true risk of adverse events, because subjects enrolled are typically healthier than the general population.[38] This is particularly true when evaluating data on patients who have diseases like AMD, because they are often elderly, and present with multiple conditions and symptoms that interact and therefore confound the trial results. The opposite of this problem may also be true, however. In trial results presented at the recent meeting of the European Society of Ophthalmology, in Amsterdam, The Netherlands,[39] patients were specifically excluded if they had had a prior stroke or cardiac event, or if they either were using, or anticipated using warfarin. Nonetheless, 2 patients in the trial experienced myocardial infarctions, 1 of which was fatal.

Lack of comparative data

Given the lack of data comparing the use of intravitreal bevacizumab with ranibizumab, there are inherent limitations in discussing treatment safety issues. There are no formal avenues for either reports or follow-up concerning adverse drug reactions (ADRs) with the ocular use of bevacizumab, although physicians are instructed to report to the drug-maker within 24 hours of ADR awareness. It is highly likely that there is under-reporting of ADRs with this off-label product.

The only truly comparative data between ranibizumab and bevacizumab will come from the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).[40] This multicentre study will enroll 1200 patients for treatment with varying regimens. Its value will be limited, however, by the fact that this is a noninferiority trial, with the predefined margin of only 5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. The trial may reveal interesting data with respect to efficacy, but as for safety measures, it is likely too small to demonstrate a statistical difference between the drugs. The number of subjects required to be enrolled to show statistically significant differences in safety between the two drugs would need to be 5000 to 10 000 subjects (5-10 times the number of patients slated for enrolment in CATT). The CATT, in its current form, will not be completed until 2011.

Conclusion

The use of intravitreal bevacizumab has recently been associated with a significant number of cases of ocular inflammation and/or sterile endophthalmitis among Canadian patients undergoing treatment for AMD. These cases were predominantly, but not exclusively limited to patients receiving treatment from a specific manufacturer's lot/batch number. Administered systemically, bevacizumab has demonstrated excellent outcomes when used to treat patients with metastatic colorectal cancer. Since late 2005, intravitreal bevacizumab has been used globally for the treatment of CNV and for the treatment of multiple retinovascular diseases, with encouraging efficacy results. The long-term safety and efficacy profiles of intravitreal bevacizumab have yet to be established. Clinically, for all anti-VEGF treatment, care should be exercised if atherothrombosis/cardiovascular disease, diabetes, or hypertension are evident and optimal evaluation and treatment for these disorders should be confirmed.[26] The fact that a significant number of cases of inflammation and/or endophthalmitis have occurred after treatment with bevacizumab is a cause for concern as clinicians search for the best treatment options with their AMD patients.

Canadian ophthalmologists who suggest therapy with intravitreal bevacizumab for CNV due to AMD should obtain a detailed informed consent documenting the following:

- That an explanation was given to their patients that there are no formal, randomized, multicentre clinical trials documenting the efficacy and safety of bevacizumab
- That information was provided regarding the recent reports of sporadic outbreaks involving clusters of patients at different institutions with severe intraocular inflammation/endophthalmitis following intravitreal use of bevacizumab
- That they highlighted that the drug is off-label and not approved for intraocular use by Health Canada, or promoted as such by Hoffmann-La Roche (the Canadian distributor) or Genentech Inc.
- And finally, that they stated that an approved therapy, ranibizumab, exists for the treatment of CNV due to AMD, and that it has proven safe and effective in large-scale clinical trials.

References

1. Rosenfeld PJ, Brown DM, Heier JS. MARINA: Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355(14):1419-1431.
2. Brown DM, Kaiser PK, Michels M. ANCHOR: Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355(14): 1432-1444.
3. Rich RM, Rosenfeld PJ, Puliafito CA. Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Retina.* 2006;26(5):495-511.
4. Rosenfeld PJ, Moshfeghi AA, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration. *Ophthalmic Surg Lasers Imaging.* 2005; 36(4):331-335.
5. Hoffmann-La Roche Ltd. Avastin® (bevacizumab) product monograph. March 27, 2009.
6. Fintak DR, Shah GK, Blinder KJ. Incidence of endophthalmitis related to intravitreal injection of bevacizumab and ranibizumab. *Retina.* 2008;28(10): 1395-1399.
7. Mason JO 3rd, White MF, Feist RM. Incidence of acute onset endophthalmitis following intravitreal bevacizumab (Avastin) injection. *Retina.* 2008;28(4): 564-567.
8. Artunay O, Yuzbasioglu E, Rasier R. Incidence and management of acute endophthalmitis after intravitreal bevacizumab (Avastin) injection. *Eye.* 2009; February 13 [Epub ahead of print].
9. Fielden MP, Nelson B, Williams RG, Ells AL, Anand J, Kherani A. Acute intraocular inflammation following intravitreal injection of bevacizumab – a cluster of cases. Paper presented at: 72nd Annual Meeting of the Canadian Ophthalmological Society; June 22, 2009; Toronto, Ontario. Abstract 1439.
10. Hall R, Lodha N, Mitchell P, Williams G, Kherani A. Incidence of ocular complications following intravitreal bevacizumab (Avastin®) injections. Paper presented at: 72nd Annual Meeting of the Canadian Ophthalmological Society; June 22, 2009; Toronto, Ontario. Abstract 1434.
11. Holland S, Ma P, Maberley D, et al. Outbreak of acute intraocular inflammation after bevacizumab intravitreal injection: An epidemiological investigation, Paper presented at: 72nd Annual Meeting of the Canadian Ophthalmological Society; June 22, 2009; Toronto, Ontario. Abstract 1444.
12. Health Canada. Reports of Eye Inflammation, Endophthalmitis, and Toxic Anterior Segment Syndrome (TASS) Following Off-label Intravitreal Use of Avastin (bevacizumab) – For Health Professionals. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/avastin_4_hpc-cps-eng.php. Accessed July 28, 2009.
13. Hoffmann-La Roche Limited. Important safety information on Avastin® (bevacizumab). Available at: http://www.cbg-meb.nl/NR/rdonlyres/66E8BACF-6328-4CAD-97F1-B546976D496B/0/AvastinDHCPonintravitrealuseFinalCHMPadoptedversion.pdf. Accessed on August 24, 2009.
14. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on pharmacy prepared ophthalmic products. *Am J Hosp Pharm.* 1993;50: 1462-1463.
15. Mamalis N, Edelhauser HF, Dawson DG. Toxic anterior segment syndrome. *J Cataract Refract Surg.* 2006;32(2):324-333.
16. Georgopoulos M, Polak K, Prager F. Characteristics of severe intraocular inflammation following intravitreal injection of bevacizumab (Avastin). *Br J Ophthalmol.* 2009;93(4):457-462.
17. Wickremasinghe SS, Michalova K, Gilhotra J, et al. Acute intraocular inflammation after intravitreous injections of bevacizumab for treatment of neovascular age-related macular degeneration. *Ophthalmology.* 2008;115(11): 1911–1915.

18. Wu L, Martínez-Castellanos MA, Quiroz-Mercado H, et al. Twelve-month safety of intravitreal injections of bevacizumab (avastin): results of the Pan-American Collaborative Retina Study Group (PACORES) *Graefes Arch Clin Exp Ophthalmol.* 2008;246(1):81-87.
19. The Royal College of Ophthalmologists. Age-Related Macular Degeneration: 2009 Guidelines for Management. Available at: http://www.rcophth.ac.uk/about/publications. Accessed July 28, 2009. Pg. 43.
20. The Royal College of Ophthalmologists. The Intravitreal Use of Bevacizumab (Avastin®) in Age Related Macular Degeneration. February 28, 2009. Available at: http://www. rcophth.ac.uk/about/publications. Accessed July 28, 2009. Pg 4.
21. General Medical Council. Prescribing off-label. GMCtoday. November/ December 2008. Available at: http://www.gmc-uk.org/publications/gmc_today/gmc_today_nov2008/prescribing_off-label.asp. Accessed on August 24, 2009.
22. Shahar J, Avery RL, Heilweil G, et al. Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin). *Retina.* 2006;26(3):262-269.
23. Bakri SJ, Snyder MR, Reid JM, Pulido JS, Singh RJ. Pharmacokinetics of intravitreal bevacizumab (Avastin). *Ophthalmology*. 2007;114:855-859.
24. Bakri SJ, Snyder MR, Reid JM, Pulido JS, Ezzat MK, Singh RJ. Pharmacokinetics of intravitreal ranibizumab (Lucentis). *Ophthalmology*. 2007;114: 2179-2182.
25. Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. *Retina*. 2006;26(8):859-870.
26. Klettner AK, Kruse ML, Meyer T, Wesch D, Kabelitz D, Roider J. Different properties of VEGF-antagonists: Bevacizumab but not Ranibizumab accumulates in RPE cells. *Graefes Arch Clin Exp Ophthalmol.* 2009; July 14 [Epub ahead of print].
27. Tuñón J, Ruiz-Moreno JM, Martín-Ventura JL, Blanco-Colio LM, Lorenzo O, Egido J. Cardiovascular risk and antiangiogenic therapy for age-related macular degeneration. *Surv Ophthalmol.* 2009;54(3):339-348.
28. Awh CC. HORIZON Extension trial of ranibizumab for neovascularization in age-related macular degeneration: first year safety/efficacy results. Paper presented at: The American Society of Retina Specialists Meeting; October 12, 2008; Maui, Hawaii.
29. Heier JS, Boyer DS, Ciulla TA, et al. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration: year 1 results of the FOCUS Study. *Arch Ophthalmol.* 2006;124(11):1532-1542.
30. Zhu X, Wu S, Dahut WL, Parikh CR. Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. *Am J Kidney Dis.* 2007;49(2):186-193.
31. Pande A, Lombardo J, Spangenthal E, Javle M. Hypertension secondary to antiangiogenic therapy: experience with bevacizumab. *Anticancer Res.* 2007;27(5B): 3465-3470.
32. Okines A, Cunningham D. Current perspective: bevacizumab in colorectal cancer – a time for reappraisal? *Eur J Cancer.* 2009;45(14):2452-2461.
33. Rasier R, Artunay O, Yuzbasioglu E, Sengul A, Bahcecioglu H. The effect of intravitreal bevacizumab (Avastin) administration on systemic hypertension. *Eye*. 2009;23(8):1714-1718.
34. Shima C, Sakaguchi H, Gomi F, et al. Complications in patients after intravitreal injection of bevacizumab. *Acta Ophthalmol.* 2008;86(4):372-376.
35. Gregori NZ, Rattan GH, Rosenfeld PJ, et al. Safety and efficacy of intravitreal bevacizumab (avastin) for the management of branch and hemiretinal vein occlusion. *Retina*. 2009;29(7):913-925.
36. Novartis Pharmaceuticals Canada Inc. Lucentis® (ranibizumab) product monograph. April 23, 2009.
37. Boyer DS. SAILOR: Meta-analysis of APTC Events in key phase II and III studies with ranibizumab in wet AMD. Paper presented at: American Academy of Ophthalmology, Retinal Sub-specialty Day; November 7, 2008; Atlanta, GA.
38. Duan Y, Mo J, Klein R, et al. Age-related macular degeneration is associated with incident myocardial infarction among elderly Americans. *Ophthalmology*. 2007;114(4):732-737.
39. Tufail A. Avastin for neovascular AMD; The ABC Trial: 1-year results of a double-masked, multi-centre, randomized study. Paper presented at: 17th Congress of the European Society of Ophthalmology; June 15, 2009; Amsterdam, the Netherlands.
40. Martin DF, Fine SL, Maguire MG, et al; National Eye Institute. Comparison of Age-Related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00593450?term=Comparison+of+Age-related+Macular+Degeneration+Treatments+Trial&rank=1. Accessed July 28, 2009.

Disclosure Statement: *Dr. Berger is a paid consultant to Novartis Pharmaceuticals Canada and he has served on advisory boards for Alcon Canada, Novartis, Allergan Canada, and Bausch & Lomb. His department receives educational and research support from Novartis and Alcon. Dr. Sharma has received honoraria from Novartis Pharmaceuticals Canada, Allergan, Pfizer Canada. He also is Chairman of the Board of Cost Effective HealthCare, and is a Director of eSight.*

SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from Novartis Pharmaceuticals Canada Inc. to support the distribution of this issue of *Ophthalmology Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Department of Ophthalmology and Vision Sciences and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party.