imaging and high-resolution SD-OCT scans may be a useful tool not only to better understand the pathogenesis of PPRCA but also to differentiate stages of the disease and to follow up patients over time.

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Emergency department visits after intravitreal bevacizumab and ranibizumab injections in diabetic patients

Bevacizumab (Avastin; Genentech, San Francisco, CA, USA) and ranibizumab (Lucentis; Genentech) are both inhibitors of vascular endothelial growth factor (VEGF). They are used intravitreally in the treatment of a variety of ocular diseases including age-related macular degeneration (AMD),[1,2] diabetic macular edema (DME),[3–7] proliferative retinopathy,[8] retinal vein occlusion,[9] and others.[10,11]

Ranibizumab was designed specifically for ocular use, whereas bevacizumab continues to be used off-label as a low-cost alternative to ranibizumab. Although both agents have shown similar efficacy in clinical studies,[12] there are important structural and functional characteristics that set them apart. Bevacizumab, a full-length anti-VEGF antibody, has slower retinal clearance and prolonged diffusion into systemic circulation when compared with ranibizumab, which is composed of only a fragment of the anti-VEGF antibody.[13]

Although the safety profiles of bevacizumab and ranibizumab have been extensively discussed in the setting of neovascular AMD,[14,15] relatively few reports have evaluated the systemic safety of these agents for the treatment of DME, the second most common indication for anti-VEGF use. The temptation has been to translate the findings from AMD trials to patients with DME. However, patients with diabetes represent a distinct cohort with multiple systemic comorbidities and, in particular, a higher predisposition for adverse cardiovascular events.[16,17] The susceptibility of this population to aberrations in the internal milieu is concerning, especially when an anti-VEGF agent like bevacizumab can linger systemically for a more substantial period.

The purpose of this study was to compare the incidence of emergency department (ED) visits within 30 days after injection of bevacizumab versus ranibizumab in patients being treated for DME.

In this retrospective chart review, we identified consecutive patients who received an intravitreal injection of bevacizumab or ranibizumab for a primary diagnosis of DME between January 2007 and January 2013 by a single retina specialist (S.S.). We excluded patients with proliferative diabetic retinopathy and patients with a primary address outside of Kingston, Ontario.

At our centre, patients generally receive ranibizumab only if they are covered under provincial or private insurance. Because of varying coverage for ranibizumab over the study period, many patients received both bevacizumab and ranibizumab at some point over their treatment course.

The primary outcome was the incidence of ≥ 1 ED visits within 30 days of injection. We considered an ED visit to have occurred if patients presented to either of the 2 EDs in Kingston (Kingston General Hospital or Hotel Dieu Hospital). For each ED visit, we recorded the diagnosis made by the ED physician and classified it

according to a Medical Dictionary for Regulatory Activities (MedDRA) subclass of ED diagnoses.[7] In addition, any hospital admission occurring as a result of the ED visit was also recorded. Proportions between groups were compared using a Fisher's exact test, and odds ratios (ORs) with a 95% confidence interval (CI).

A total of 300 patients received intravitreal bevacizumab or ranibizumab for a primary diagnosis of DME between January 2007 and January 2013. Of these, 159 patients were excluded for having a primary address outside of Kingston, leaving a sample size of 141 patients. Patients received an average of 13.5 injections over the study period, for a total of 581 bevacizumab injections and 1322 ranibizumab injections. Nineteen patients received solely bevacizumab, whereas 60 received solely ranibizumab, and 62 received both agents over the study period.

Demographics of patients at each injection are listed in Table 1. One or more ED visits occurred after 39 of 581 (6.7%) bevacizumab injections compared with 71 of 1322 (5.4%) ranibizumab injections (OR 1.3 [95% CI 0.85–1.9], $p = 0.29$). When separated by MedDRA diagnosis subclass, no significant differences were observed with the exception of skin and subcutaneous disorders, which were more common after bevacizumab injections ($p = 0.009$). A similar proportion of ED visits resulted in a hospital admission for both the bevacizumab and the ranibizumab groups (12/39 [30.8%] vs 20/71 [28.2%], $p = 0.83$).

When evaluating the systemic safety of any given therapeutic agent, it is necessary to assess the acute effect of the agent within a time frame that the agent is expected to act in vivo. After intravitreal injection, bevacizumab can last up to 3 weeks in the general circulation, compared with just a few hours with ranibizumab.[18] Several studies have demonstrated that bevacizumab results in a significantly greater inhibition of serum VEGF compared with ranibizumab.[19–22] Therefore, it is prudent to determine whether patients with diabetes are at an overtly increased risk for adverse systemic events within the period where serum levels would be altered by bevacizumab. We aimed to address this by comparing the incidence of ED visits within 30 days of injection with bevacizumab versus ranibizumab in patients being treated for DME.

In our retrospective cohort study, we were unable to detect any statistically significant difference in the incidence of ED visits in the bevacizumab group and the ranibizumab group. Although we were limited by tracking only ED visits, and hence not able to capture all potential systemic adverse events, our results provide some reassurance that bevacizumab does not considerably increase the risk for acute systemic complications in patients being treated for DME, when compared with ranibizumab.

The utility of our study was that it provides data on the *acute* systemic effects after anti-VEGF injection for DME. However, most patients with DME require frequent retreatment over several years. One concern is that the continual suppression of basal levels of serum VEGF, especially with bevacizumab, could disrupt the physiologic response to tissue ischemia.[23,24] This may be particularly detrimental in patients with diabetes, who in addition to being at a greater risk for cardiovascular disease,[16] tend to have higher morbidity and mortality after myocardial infarctions.[25] This population is also known for asymptomatic "silent" myocardial infarctions,[26] meaning that the clinician may not have the opportunity to halt bevacizumab injections after an ischemic event. If serum VEGF levels have been chronically suppressed, beneficial reperfusion of damaged myocardium via neovascularization might be affected.

Several studies have demonstrated trends toward an increased long-term risk for thromboembolic events in

Table 1——Patient demographics and incidence of emergency department visits within 30 days of intravitreal injection with bevacizumab or ranibizumab for diabetic macular edema

Demographics	Bevacizumab (n = 581 injections)	Ranibizumab (n = 1322 injections)	*p*
Mean age at injection, yr	66.4	67.3	0.13
Sex (% female)	60.9	51.8	0.01
ED visits, n	44	72	0.08
Injections that were followed by ≥1 ED visits, n (% of total injections)	39 (6.7%)	71 (5.4%)	0.29
Rate of hospital admission	12/39 (30.8%)	20/71 (28.2%)	0.83
Mean length of hospital admission, days	6.1	8.8	0.34
ED visits grouped according to MedDRA subclass of diagnosis, n			
Cardiac	4 (0.7%)	8 (0.6%)	0.76
Ear	0	1 (0.1%)	1.0
Gastrointestinal	5 (0.9%)	8 (0.6%)	0.55
General conditions	5 (0.9%)	7 (0.5%)	0.53
Hepatobiliary	0	1 (0.1%)	1.0
Infections	3 (0.5%)	13 (1.0%)	0.42
Injuries	5 (0.9%)	6 (0.5%)	0.33
Metabolic and nutritional	4 (0.7%)	6 (0.5%)	0.51
Musculoskeletal	4 (0.7%)	5 (0.4%)	0.47
Nervous system	1 (0.2%)	6 (0.5%)	0.68
Psychiatric	0	2 (0.2%)	1.0
Renal and urinary	2 (0.3%)	2 (0.2%)	0.59
Respiratory	5 (0.9%)	3 (0.2%)	0.06
Skin and subcutaneous	4 (0.7%)	0	**0.009**
Vascular	2 (0.3%)	4 (0.3%)	1.0

ED, emergency department.
p value shown in bold is statistically significant.

patients with diabetes receiving anti-VEGF agents. After 36 months of follow-up in the RISE/RIDE trial, patients in the high-dose ranibizumab group were at an increased risk for systemic adverse events, including thromboembolic events, compared with the low-dose or sham group.[27] Similarly, although the BOLT study was underpowered to detect safety differences and also excluded patients with high-risk cardiovascular features, there was still a detectable trend toward more myocardial infarctions in the bevacizumab group (2/42 patients) compared with the laser group (0/38 patients) at 24-month follow-up.[28]

These studies reflect a gap in the literature pertaining to DME and anti-VEGF therapy, as there are currently no direct comparative trials between bevacizumab and ranibizumab sufficiently large enough to detect the safety differences between these 2 agents.

Overall, our study represents one of the largest series of anti-VEGF injections for DME in the literature. Although our findings lend support to the systemic safety of bevacizumab in the acute period after injection, randomized control trials with long-term follow-up are required to understand the repercussions of chronic anti-VEGF use for the treatment of DME.

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