## Peripapillary RNFL thickness in nonexudative versus chronically treated exudative age-related macular degeneration

*Dear Editor:*

We read with interest the paper "Peripapillary RNFL thickness in nonexudative versus chronically treated exudative age-related macular degeneration" written by Yau et al.[1] They have reported no deleterious effect of multiple anti–vascular endothelial growth factor injections on retinal nerve fibre layer (RNFL) in patients with wet age-related macular degeneration (AMD) in comparison to noninjected fellow eyes with dry AMD. Interestingly, they observed a higher mean RNFL thickness value in injected eyes, which was solely related to thickening in the temporal quadrant. They related this finding to the spread of macular edema to the peripapillary area. We want to congratulate the authors on these valuable observations; however, some issues need to be raised concerning the current study.

It has been recently showed that RNFL measurements need to be adjusted according to the axial length of the eye.[2] No data are presented regarding the refractive status of the patients in the current study. Moreover, Lee and Yu showed significant thinning in RNFL but no other significant change in other optic nerve head parameters in dry AMD eyes when compared with control eyes, which is lacking in the current study.[3] Therefore, RNFL thickness comparisons between wet and dry AMD eyes should be interpreted cautiously.

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*Can J Ophthalmol* 2016;51:233
0008-4182/16/$-see front matter © 2016 Canadian Ophthalmological Society.
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http://dx.doi.org/10.1016/j.jcjo.2016.02.016

## Canadian preference and trends survey results for anti-VEGF treatment of macular edema

The treatment of macular fluid from neovascular age-related macular degeneration (AMD), diabetic macular edema (DME), and vein occlusion is evolving as new treatment modalities develop and research outcome results become available. Intravitreal injection of anti–vascular endothelial growth factor (anti-VEGF) agents has become one of the most common procedures performed by the retina specialist in the treatment of AMD, retinal vein occlusion (RVO), and DME. In 2009 and 2013, Health Canada estimated the number of prescriptions dispensed by pharmacies for bevacizumab and ranibizumab to be 24 504 and 338 889, respectively.[1] Despite the increased use of these agents, there is no Canadian consensus regarding optimal technique, specific indications, agent of choice, second-line agents, treatment interval, and follow-up protocols. There is emerging evidence supporting the use of aflibercept (Eylea; Regeneron Pharmaceuticals) for AMD,[2–5] RVO,[6–8] and DME.[9,10] However, the role of aflibercept as a first-line treatment or second line for recalcitrant cases compared to ranibizumab (Lucentis; Genentech) and bevacizumab (Avastin; Genentech) remains unclear. Although the existing literature has explored practice patterns of anti-VEGF use,[11–15] there are no clear guidelines in Canada. This is particularly true with rapidly expanding treatment indications and treatment options. To date, only 2 Canadian studies have examined anti-VEGF techniques, but this report predates the introduction of aflibercept into the market.[11,15]

Our report describes the 2015 practice patterns relating to anti-VEGF usage in the treatment of macular edema secondary to neovascular AMD, DME, and RVO by Canadian retina specialists. The patterns of anti-VEGF usage reflect clinical evidence, provincial funding models and individual clinical preferences.

### Methods

The executive committee of the Canadian Retina Society sent a national questionnaire, known as the Canadian Preference and Trends (CAN-PAT) Survey, via email to all members of the Canadian Retina Society. This 65-question survey focused on the surgical and medical treatment of retinal disease and was developed without industry funding or input. The online survey was voluntary and anonymous. Reminder emails were sent to

maximize participation. The survey was completed and closed in February 2015. This article provides a summary of the intravitreal injection-related responses for AMD, DME, and RVO.

## Results

### Survey participants

Of 118 Canadian retina specialists, 76 completed the survey with participation by individuals in all provinces. The majority of respondents had been in practice for at least 8 years (60.5%).

### Intravitreal injection procedure

Topical anaesthesia was the most common (77.6%) form of anaesthesia for intravitreal injections, while bilateral injections were often performed on the same day (75.0%). Many Canadian retina specialists (43.4%) would examine anti-VEGF patients at the slit lamp before each injection, whereas 31.6% do so every 3 months.

### Age-related macular degeneration

Retina specialists rely primarily (98.7%) on clinical examination and optical coherence tomography (OCT) to identify wet AMD (wAMD). Many retina specialists no longer perform fluorescein angiography as part of the initial diagnostic evaluation for patients with neovascular AMD (40.8%). The majority of retina specialists (85.5%) presently do not order genetic testing for patients with wet macular degeneration.

Ranibizumab was the most common first-line agent in the treatment of wAMD (73.7%), followed by bevacizumab (23.7%) and aflibercept (2.6%). Most retina specialists (61.8%) believed that aflibercept covered the broadest range of neovascular AMD types, whereas 47.4% of respondents reported that, of the 3 available anti-VEGF agents, all were equally effective at decreasing subretinal and intraretinal fluid. In cases of persistent wAMD after 8 monthly injections (and vision 20/50), the majority of specialists (73.7%) would attempt a trial of an alternate anti-VEGF agent. Of the respondents, 52.6% believed that aflibercept provided the longest treatment interval in eyes with neovascular AMD. Aflibercept was also felt to be relatively good in the treatment of serous PEDs, with 34.2% of retinal specialists believing that it could successfully flatten a serous PED that had failed ranibizumab/bevacizumab.

### Diabetic retinopathy

On average, most respondents (68.4%) stated that they would inject an anti-VEGF agent approximately 7 to 9 times in the first year of treatment for DME. When asked about first-line treatment for a new phakic diabetic patient with 20/50 vision and DME, 63.2% of retinal specialists would inject ranibizumab and 32.9% would inject bevacizumab. In cases of refractory DME, where patients have received focal laser and at least 6 prior ranibizumab injections, 46.1% of respondents would employ intravitreal triamcinolone acetonide, 19.7% would try aflibercept, and 14.5% would try the dexamethasone implant. In phakic patients with clinically significant DME (CSME), but with good vision (20/25) and central fluid on OCT, 57.9% physicians would inject an intravitreal anti-VEGF agent, whereas 27.6% would observe and a small subset (6.6%) would try micropulse laser. In contrast, in a phakic patient with central DME and 20/50 vision, 98.7% of respondents would use anti-VEGF. Ranibizumab (63.9%) was the agent most commonly utilized, followed by bevacizumab (32.9%) and aflibercept (2.6%).

### Retinal vein occlusions

The CAN-PAT survey revealed that most retinal specialists would treat a central RVO (CRVO) with vision-affecting macular edema with ranibizumab (61.8%), bevacizumab (35.5%), or aflibercept (2.6%). Similar results for branch RVO (BRVO) with macular edema (ranibizumab 51.3%, bevacizumab 43.4%, and aflibercept 1.3%) were observed. None of the respondents listed grid laser as first-line therapy for BRVO. However, 53.9% would use it after stabilizing macular edema with an anti-VEGF or steroid agent, or use it in combination with an anti-VEGF injection (15.8%), whereas 26.3% do not use it at all.

When dealing with macular edema from BRVOs that are unresponsive to bevacizumab, 46.1% of respondents would treat with ranibizumab, 27.6% would utilize intravitreal triamcinolone acetonide, 7.9% would try intravitreal dexamethasone implant (Ozurdex; Allergan), and 5.3% would choose aflibercept. In eyes with persistent macular edema after 6 monthly anti-VEGF injections and peripheral ischemia on fluorescein angiography, 64.5% of respondents would add sector panretinal photocoagulation with anti-VEGF, whereas 14.5% would try intravitreal triamcinolone acetonide only. When asked which treatment allows the longest interval between repeat injections, 50% of retinal specialists believe that the dexamethasone implant is the best, followed by aflibercept (13.2%) and intravitreal triamcinolone acetonide (11.8%).

## Discussion

At the time of the CAN-PAT survey, ranibizumab was covered by all 10 provincial drug benefit plans for wAMD, whereas only 8 of 10 for DME, 6 of 10 for BRVO, and 7 of 10 for CRVO. Bevacizumab was covered by 1 of 10 provinces and Aflibercept was not covered by any provincial drug benefit program at the time of the conclusion of the survey.[16–31]

### Age-related macular degeneration

Anti-VEGF therapy is the current mainstay for the treatment of wAMD. The anti-VEGF Antibody for the

Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) trial and the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) showed that continuous monthly intravitreous injections of ranibizumab for 2 years resulted in significant gains in visual acuity.[32–34] In the Comparison of AMD Treatment Trials, bevacizumab and ranibizumab in both continuous monthly and as-needed treatment regimens resulted in equivalent vision outcomes over a 2-year period.[35] The large parallel VIEW 1 and VIEW 2 studies investigating aflibercept for subfoveal neovascular AMD also found it to be noninferior to ranibizumab.[4,5]

According to our CAN-PAT survey, the most common first-line anti-VEGF agent for wet AMD was ranibizumab (73.7%) followed by bevacizumab (23.7%) and aflibercept (2.6%). These usage patterns reflect current provincial funding for anti-VEGF agents. As the majority of respondents felt that aflibercept treated the widest range of wAMD subtypes and provided the longest effect, it is likely that its use will increase significantly once provincial coverage becomes available.

### Diabetic macular edema

Canadian retina specialists utilize anti-VEGF injections as first-line therapy to treat DME in keeping with current evidence.[36–38] A recent study from the Diabetic Retinopathy Clinical Research Network suggests that all 3 anti-VEGF agents are effective and equivalent for mild vision loss ($\geq$20/50); however, aflibercept may be superior in eyes with worse vision ($<$20/50).[9] Despite these data, ranibizumab remains the most frequently used agent. Furthermore, although in an American model bevacizumab may be superior in terms of cost effectiveness and patient willingness to pay,[39] ranibizumab remains more frequently used in Canada. The Canadian results were consistent with provincial funding for anti-VEGF medication at the time of the survey. It is likely that the use of anti-VEGF agents will change significantly as funding becomes available for aflibercept and bevacizumab across Canada.

Although there is evidence to support the use of intravitreal steroids[40,41] and aflibercept[10] in DME, there is no clear consensus in the existing literature as to their use as first-line therapy or for recalcitrant cases. Interestingly, in patients refractory to ranibizumab, intravitreal triamcinolone acetonide (46.1%) was preferred to aflibercept (19.7%).

### Retinal vein occlusion

The Central Retinal Vein Occlusion (CRUISE) and Branch Retinal Vein Occlusion (BRAVO) studies demonstrated efficacy of ranibizumab for macular edema related to RVO.[42,43] Consistent with recent Canadian expert consensus guidelines,[44] this survey demonstrated that anti-VEGF is now the favoured first-line treatment. A similar survey performed by the American Society of Retina Specialists (ASRS) for global trends in anti-VEGF use in 2015 found comparable results. In this survey, as-needed treatment with anti-VEGF injections were the mainstay of treatment for visually significant macular edema secondary to RVO.[45] Ranibizumab was the preferred anti-VEGF agent for both CRVO and BRVO; however, the dexamethasone implant for RVO was felt to have the longest treatment interval. A minority of retinal specialists in this survey used aflibercept as first-line therapy. A recent review comparing ranibizumab and aflibercept in the treatment of macular edema secondary to RVO found that both groups had a similar interval between injections and received a similar number of injections.[46]

## Conclusions

The results of this survey regarding practice patterns pertaining to anti-VEGF usage are consistent with published randomized clinical trials and reflect the realities of the Canadian health-care system, where provincial funding may influence treatment patterns. It is likely that the use of aflibercept, bevacizumab, and dexamethasone implants may change with provincial funding for these and other newer agents.

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**Disclosure:** The authors have no proprietary or commercial interest in any materials discussed in this article.

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*Can J Ophthalmol* 2016;51:233–237
0008-4182/16/$-see front matter © 2016 Published by Elsevier Inc on behalf of the Canadian Ophthalmological Society.
http://dx.doi.org/10.1016/j.jcjo.2015.10.014

## Canadian Retina Society ocular safety and therapeutics update: hemorrhagic occlusive retinal vasculitis

On behalf of the Canadian Retina Society (CRS), we are writing to you regarding an important safety concern with the use of intracameral vancomycin. Recently, there have been several cases of postoperative hemorrhagic occlusive retinal vasculitis (HORV) that have emerged both in Canada and in the United States after uncomplicated cataract surgery after intracameral vancomycin injection. These cases represent eyes that appear normal during the early postoperative period (up to 14 days) and subsequently develop a progressive painless loss of vision.[1] Diffuse ischemia, significant retinal hemorrhaging, and retinal vasculitis are the hallmarks of this condition. Several bilateral cases have been also reported. The CRS is working to learn more about the prevalence and severity of this entity by collecting data on reported cases nationwide to be included for publication. If your readers have a case of HORV, we encourage you to share it with the CRS at crssafteycc@gmail.com and participate in the authorship of this report.

**Canadian Retina Society Executive Board**

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*Can J Ophthalmol* 2016;51:237
0008-4182/16/$-see front matter © 2016 Published by Elsevier Inc on behalf of the Canadian Ophthalmological Society.
http://dx.doi.org/10.1016/j.jcjo.2016.04.019