Canadian Retina Society (CRS) Position Paper on the Necessity of

Sustained Funding to Ensure Continued Access to Anti-Vascular Endothelial Growth Factor Drugs to Preserve Vision for Canadians living with Retinal Diseases

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***Introduction*:**

Neovascular age-related macular degeneration (nAMD), also known as exudative AMD or "wet" AMD, is the leading cause of central vision loss in patients over the age of 65 in Canada (1). The disease burden of nAMD is projected to increase in step with the major demographic shift of accelerated aging that is underway in Canada and in most developed nations around the world. The increasing number of patients with nAMD will accordingly place increased demand on health care systems as the need for treatment grows. The natural history of nAMD is well described (2-4). Untreated, or under-treated, nAMD progresses rapidly, resulting in severe and permanent central visual loss and possibly legal blindness (4). Vision loss from nAMD causes significant morbidity in patients, especially in those who have restricted access to prompt care. Maintaining vision in the elderly is critical to improved quality of life and decreased morbidity and mortality from falls. The most recent analysis of the financial burden on vision loss and visual impairment in Canada

published in 2011 estimates the total cost of visual impairment at greater than $15.8 billion CAD per annum (8). Of the $15.8 billion, approximately 55% represents the direct health system expenditure ($8.6 billion per annum), with the remaining 45% representing loss in productivity, losses from taxation, welfare etc. and the remainder being disability, death and other indirect costs (8). The authors of this report estimated the total financial burden to be approximately $20 000 per person with vison loss per annum (8); which, likely is an under estimate based on the cost of living in 2019. Current estimates suggest that by 2032, 1 in 4 Canadians will be affected by eye disease, with costs in in excess of $32 billion (8). In Canada, over 1 million individuals currently have early AMD, and greater than 250,000 have advanced forms of the disease (9).

In addition to AMD, diabetic macular edema (DME) represents another common cause of vision loss from retinal disease. In fact, DME is the most common cause of vision loss amongst working aged individuals in Canada (10). DME results from a breakdown in the blood-retina barrier, resulting in the leakage of fluid into the central retina, with swelling and exudation and reduced visual acuity. As the prevalence and incidence of diabetes in Canada continues to increase the burden of visual impairment secondary to DME will also grow.

Current Treatment of Neovascular Age Related Macular Degeneration :

Currently the standard of care for nAMD treatment is intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents (11). At present, there are three commercially available anti-VEGF therapies used by retina specialists to treat nAMD: Ranibizumab (Lucentis®, Novartis Pharmaceuticals Canada), Aflibercept (Eylea®, Bayer Inc.), and off-label Bevacizumab (Avastin®, Hoffmann-La Roche Ltd.). Bevacizumab is not approved by Health Canada for the treatment of nAMD; however, it is commonly used off-label for the treatment of retinal neovascular conditions such as nAMD, DME and retinopathy of prematurity.

Ranibizumab was the first of the current anti-VEGF treatments to demonstrate a significant treatment effect for nAMD. Pooled analysis from the ANCHOR (2006), MARINA (2006), and PIER (2008) trials demonstrates a consistent gain of 15 or more letters (3 lines of visual acuity) in visual acuity at one year of treatment compared to sham controls or verteporfin photodynamic therapy (PDT) (13). In addition patients treated with ranibizumab were significantly less likely to lose 15 or more letters at 2 years compared to sham or PDT (13). Importantly, this Cochrane Review found that ranibizumab resulted in fewer cases of blindness compared with standard of care sham or PDT at one and two years (13).

A meta-analysis of the 4 major international multicenter randomized clinical trials looking at anti-VEGF therapy for nAMD, the CATT (2011), IVAN (2013), GEFAL (2013), and MANTA (2013) trials, demonstrated similar outcomes for bevacizumab vs. ranibizumab with respect to a gain of 15 letters or more at 1 year (13). Pooled analysis of the VIEW1 and VIEW2 trials comparing aflibercept with ranibizumab demonstrate that improvement in vision (gain of 15 letters) and stability of vision and visual acuity are similar between the two treatments at one and two years, and have a similar safety profile (14).

***Anti-VEGF therapy and Diabetic Macular Edema*:**

Over the past 10 years, numerous major multi-center, randomized clinical trials have consistently and repeatedly demonstrated the unsurpassed superiority and safety of anti-VEGF therapy as the standard-of-care in the management of center-involving DME (18-20). Patients treated with anti-VEGF medications are significantly more likely to gain vision and less likely to lose vision over the near and long-term (18, 20). In addition, anti-VEGF treatment has been shown to both prevent progression of diabetic retinopathy and reduce its severity (21, 22). A Cochrane Review meta-analysis of 18 studies investigating the role of anti-VEGF treatment for DME

concluded that there is high-quality evidence that anti-VEGF treatment is superior to conventional treatment alone (i.e., focal laser photocoagulation) (10).

Funding issues currently effecting Canadians:

The efficacy of anti-VEGF therapy in treating patients with nAMD and DME is incontrovertible. However, the treatment success does come at a financial cost. The two-year treatment cost of ranibizumab is approximately $16 000 to $39 000 CAD per person depending on the dosing and the two-year treatment cost of aflibercept is approximately $19 000 CAD per person (12). Most patients require greatly more than two years of anti-VEGF injections to maintain optimal acuity. Currently in most Canadian provinces anti-VEGF treatments are reimbursed by provincial drug benefit plans, with specific inclusion criteria (e.g. age > 65 years in Ontario for on-label therapy). Many provincial governments are re-evaluating their reimbursement programmes in an attempt to manage costs. For example, some Provinces (Manitoba and Newfoundland) have limited the total number of lifetime treatments reimbursed by the Government to 15 doses per patient (not per eye). The background for this seemingly arbitrary number of 15 doses comes from a 2014 report by the Canadian Expert Drug Advisory Committee (CEDAC) (23). Unfortunately, this outdated report only included 1 randomized control trial (CATT (24)) and one open-labeled trial (HORIZON (25)) in their analysis, drawing a conclusion that the value of "more than 15 injections" was "unclear" (23). The report from the CEDAC does not adequately capture the quality of life value of anti-VEGF treatment nor is it in-depth enough to make a statement regarding policymaking. The document does not explain why studies were excluded from analysis and the consensus of what papers were used for analysis were selected by only one person (23). The CEDAC review of the CATT (24) and HORIZON (25) studies uses the PRN dosing numbers for ranibizumab (12.6 injections) and bevacizumab (14.1 injections) as the end point for success.

However, even in the CEDAC document it is stated that the results of the CATT demonstrate that PRN dosing was less effective compared to monthly dosing with respect to visual gains or maintaining visual acuity over the 2 year period (23). Deriving a maximum of 15 injections based on this interpretation of the CATT and HORIZON trials is inherently flawed and dangerous. Data from the HORIZON trial demonstrated that PRN dosing led to increased need for monthly monitoring to ensure the patient did not require additional dosing, leading to increased burden of office visits (25). Importantly, non-adherence to the strict monthly monitoring lead to regression of the previous treatment gains and visual decline (25). More recent data from the AURA study clearly demonstrates that patients who received greater than 7 injections over 1 year or greater than14 injections over 2 years gained more letters of visual acuity and demonstrated greater vision maintenance than patients receiving fewer injections (26). This finding underpins the need for appropriate data analysis for policy makers and the dangers of relying on only a few studies to make important funding decisions for Canadians.

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) is the organization that provides national guidance and advice to improve health care. The NICE 2018 (42) guidelines on anti-VEGF treatment for nAMD outlines that intravitreal anti-VEGF treatment is the treatment of choice and should be continued so long as there is evidence of disease activity, regardless of the duration (ie. No limit on number of injections). They state that this treatment is "clinically effective" and "cost effective". Similarly, for Diabetic Macular Edema, the NICE 2013 guidelines state that intravitreal anti-VEGF treatment is recommended for treating visual impairment due to diabetic macular oedema and that this treatment should be continued until their clinician considers it appropriate to stop. There are no stipulations of maximal numbers of injections as the evidence strongly argues against any limits on lifetime doses.

We know from the natural history of nAMD that progression without treatment is inevitable. Shah et al., (2009 demonstrated a significant relationship between the number of letters lost (decrease in vision) and the number of months of untreated exudative disease ($r^2 = 0.98$) (2). This is further supported by data from Liu et al., (2013) that a choroidal neovascular lesion will progress without treatment and that the lesion will reach half of its maximum size within 14 months after onset of exudation (27) – leading to significant and irreversible vision loss within 1-3 years of disease onset (4). An important factor in the seemingly arbitrary cap of 15 injections is the fact the CEDAC report did not address the rates of recurrence with stopping of treatment. This is a very concerning issue for patients and retinal specialists who care for these patients. It is clear from the literature that stopping treatment is associated with visual decline, loss of treatment gains, neovascular lesion size progression, and increased exudation leading to permanent visual impairment (13, 24, 25, 28, 29). In fact, a recent report by Hwang et al. (2019) demonstrated that many patients who stop treatment after successful resolution of exudation show recurrence of nAMD exudation in as early as 4 months after treatment cessation (30). In that study, patients who extended treatment intervals out to 12 weeks had a 10% chance of recurrence of exudation per year, suggesting the majority of patients will require more frequent dosing than q12weeks and those who stop treatment altogether will have a significant risk of disease recurrence (30). Data from these studies and others demonstrates significant vision loss and regression of gains in patients that stop treatment; whether due to patient fatigue, loss to follow-up or difficulty with access to care for financial or other reasons. Moreover, it is not only important to follow these patients closely, but also to provide them with timely and easy access to anti-VEGF medications if recurrence is detected. The same is true for patients suffering from DME. We know from studies looking at

patients lost to follow-up after a course of anti-VEGF for DME that up to 77% of patients lost significant vision (>3lines) and 46% of those end up with vision of hand motion or worse (19). Recent data from Wubben et al. (2019) demonstrated that patients with DR treated with anti-VEGF who experience treatment interruptions (for whatever reason) are at very high risk for irreversible vision loss (19). The visual outcomes of anti-VEGF treatment are superior to retinal photocoagulation for both DME and proliferative diabetic retinopathy (10, 21, 31), and so providing ready and uninterrupted access to these medication is critical for preventing irreversible vision loss in this patient group. The studies chosen by the CEDAC for review of the effectiveness of anti-VEGF simply do not capture these issues, and so we strongly urge those provincial government funding agencies that limit drug injections numbers to reconsider this decision. Furthermore, limiting lifetime treatments to 15 injections does not account for patients who have not yet stabilized, who are not responding to a particular agent, and those who develop nAMD (or DME) in their fellow eye. Data from 7-year follow-up studies demonstrate clearly that visual acuity is maintained in most patients with long-term treatment (32, 33). Importantly, this number does not reflect the progression to nAMD in the fellow eye. A meta-analysis by Wong et al. (2008) demonstrated nAMD developed in the fellow eye in approximately 12% of patients within one year of being diagnosed with nAMD and in 27% of patients by 4 years (3). 7-year follow-up data reported in the SEVEN-UP study demonstrate that 50% of patients go on to develop nAMD in the fellow eye that was initially dry (34). Based on this data, approximately a half or more of patients with nAMD in one eye only will progress to nAMD in the fellow eye within a few years, requiring additional anti-VEGF treatments. For those patients limited to 15 “covered” injections in total, it would require a significant out-of-pocket expense or worse, the decision not to treat based on financial constraints. We know from more recent long-term data that patients treated for 8 years

with over 50 injections have been shown to have and maintain significant gains in ETDRS letter visual acuity (2-3-line gain on average) with very low rates of complications (35). Similarly for DME, studies have clearly shown that continued therapy optimizes outcomes in the long-term (40, 41). These are outcomes not achievable with previous nAMD or DME treatments. It is simply unacceptable in 2019 in Canada to limit lifetime reimbursed injections to 15 doses, as it forces the patient or their family to decide whether they need to incur significant debt or else not treat, thereby allowing a vision-threatening condition to progress to irreversible legal blindness.

Considering the growing financial expense to public and private health systems, as well as the burden of treatment for both the patients and the treating physician, several strategies have been investigated by ophthalmologists and researchers to address limiting the total number of treatments required for successful treatment. Several variations of *pro re nata* (PRN or as-needed) dosing and treat-and-extend regimens have been studied (HORIZON (25), TREX-AMD (36-38), CAN-TREAT (29), (35)). Together data from these large trials demonstrates that patients treated with a treat-and-extend regimen have similar visual outcomes as patients on monthly treatment but require on average 2-4 less injections per year, which translates to a direct savings to the healthcare system on over $4000 per patient.

Conclusions:

It is clear that the number of Canadians living with nAMD and DME is on the rise and that treatment of these vision-threatening diseases may cause a significant burden on the patient, caregivers and the broader healthcare system as a whole (1, 5, 8). The global prevalence of AMD is estimated to exceed 196 million people by 2020 and projected to reach a staggering 288 million people by 2040 (1). Clearly strategies will need to be implemented to account for the increased need for treatment. However, limiting funding for anti-VEGF therapy or arbitrarily limiting the

number of injections to prespecified number is misguided, injudicious, and inappropriate and runs contrary to level-1 medical evidence as well as published and widely accepted evidence-based guidelines (8).

Compared to the rest of the world, Canada has a relatively low rate of low vision and blindness. This is, in part, due to the access to universal healthcare and coverage of medications to treat vision-threatening conditions such as nAMD and DME.

We hope that provincial and federal stakeholders will have continued open dialogue with retina specialists to developed evidence-based strategies to support anti-VEGF therapy for Canadians. The Canadian Retina Society and the Canadian Ophthalmological Society are eager to participate in any discussions on any topics related to the vision health of all Canadians.

References:

1. Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2(2):e106-16.

2. Shah AR, Del Priore LV. Natural history of predominantly classic, minimally classic, and occult subgroups in exudative age-related macular degeneration. Ophthalmology. 2009;116(10):1901-7.

3. Wong TY, Wong T, Chakravarthy U, Klein R, Mitchell P, Zlateva G, et al. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. Ophthalmology. 2008;115(1):116-26.

4. Polito A, Isola M, Lanzetta P, Gregori D, Bandello F. The natural history of occult choroidal neovascularisation associated with age-related macular degeneration. A systematic review. Ann Acad Med Singapore. 2006;35(3):145-50.

5. Prenner JL, Halperin LS, Rycroft C, Hogue S, Williams Liu Z, Seibert R. Disease Burden in the Treatment of Age-Related Macular Degeneration: Findings From a Time-and-Motion Study. Am J Ophthalmol. 2015;160(4):725-31.e1.

6. Yuzawa M, Fujita K, Tanaka E, Wang EC. Assessing quality of life in the treatment of patients with age-related macular degeneration: clinical research findings and recommendations for clinical practice. ClinOphthalmol. 2013;7:1325-32.

7. Maberley DA, Hollands H, Chuo J, Tam G, Konkal J, Roesch M, et al. The prevalence of low vision and blindness in Canada. Eye (Lond). 2006;20(3):341-6.

8. Cruess AF, Gordon KD, Bellan L, Mitchell S, Pezzullo ML. The cost of vision loss in Canada. 2. Results. Can J Ophthalmol. 2011;46(4):315-8.

9. Cruess AF, Berger A, Colleaux K, Greve M, Harvey P, Kertes PJ, et al. Canadian expert consensus: optimal treatment of neovascular age-related macular degeneration. Can J Ophthalmol. 2012;47(3):227-35.

10. Virgili G, Parravano M, Menchini F, Evans JR. Anti-vascular endothelial growth factor for diabetic macular oedema. Cochrane Database Syst Rev. 2014(10):CD007419.

11. Society CO. Eye Conditions, Disorders and Treatments: Age-related macular degeneration (AMD) 2018 [Available from: http://www.cos-sco.ca/vision-health-information/conditions-disorders-treatments/retinal-diseases/amd/.

12. Review CT. Anti–vascular endothelial growth factor drugs for the treatment of retinal conditions — recommendations report. In: review) Ct, editor. Ottawa, Canada: CADTH; 2016.

13. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2019;3:CD005139.

14. Sarwar S, Clearfield E, Soliman MK, Sadiq MA, Baldwin AJ, Hanout M, et al. Aflibercept for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2016;2:CD011346.

15. Report TPMI. Market Intelligence Report: Anti-Vascular Endothelial Growth Factor (Anti-VEGF) Drugs for Retinal Conditions, 2017. Ottawa, Canada2017.

16. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol. 1985;103(12):1796-806.

17. Qaum T, Xu Q, Joussen AM, Clemens MW, Qin W, Miyamoto K, et al. VEGF-initiated blood-retinal barrier breakdown in early diabetes. Invest Ophthalmol Vis Sci. 2001;42(10):2408-13.

18. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012;119(4):789-801.

19. Wubben TJ, Johnson MW, Group A-VTIS. Anti-VEGF Therapy for Diabetic Retinopathy: Consequences of Inadvertent Treatment Interruptions. Am J Ophthalmol. 2019.

20. Virgili G, Parravano M, Evans JR, Gordon I, Lucenteforte E. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. Cochrane Database Syst Rev. 2018;10:CD007419.

21. Ip MS, Domalpally A, Sun JK, Ehrlich JS. Long-term effects of therapy with ranibizumab on diabetic retinopathy severity and baseline risk factors for worsening retinopathy. Ophthalmology. 2015;122(2):367-74.

22. Ip MS, Domalpally A, Hopkins JJ, Wong P, Ehrlich JS. Long-term effects of ranibizumab on diabetic retinopathy severity and progression. Arch Ophthalmol. 2012;130(9):1145-52.

23. (CEDAC) CEDAC. Long-Term Use of Ranibizumab for the Treatment of Age-Related Macular Degeneration: A Review of the Clinical and Cost-Effectiveness and Guidelines. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2014.

24. Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012;119(7):1388-98.

25. Singer MA, Awh CC, Sadda S, Freeman WR, Antoszyk AN, Wong P, et al. HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. Ophthalmology. 2012;119(6):1175-83.

26. Holz FG, Tadayoni R, Beatty S, Berger A, Cereda MG, Hykin P, et al. Key drivers of visual acuity gains in neovascular age-related macular degeneration in real life: findings from the AURA study. Br J Ophthalmol. 2016;100(12):1623-8.

27. Liu TY, Shah AR, Del Priore LV. Progression of lesion size in untreated eyes with exudative age-related macular degeneration: a meta-analysis using Lineweaver-Burk plots. JAMA Ophthalmol. 2013;131(3):335-40.

28. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2014(8):CD005139.

29. Kertes PJ, Galic IJ, Greve M, Williams RG, Rampakakis E, Scarino A, et al. Canadian Treat-and-Extend Analysis Trial with Ranibizumab in Patients with Neovascular Age-Related Macular Disease: One-Year Results of the Randomized Canadian Treat-and-Extend Analysis Trial with Ranibizumab Study. Ophthalmology. 2019.

30. Hwang RY, Santos D, Oliver SCN. RATES OF EXUDATIVE RECURRENCE FOR EYES WITH INACTIVATED WET AGE-RELATED MACULAR DEGENERATION ON 12-WEEK INTERVAL DOSING WITH BEVACIZUMAB THERAPY. Retina. 2019.

31. Bressler SB, Beaulieu WT, Glassman AR, Gross JG, Jampol LM, Melia M, et al. Factors Associated with Worsening Proliferative Diabetic Retinopathy in Eyes Treated with Panretinal Photocoagulation or Ranibizumab. Ophthalmology. 2017;124(4):431-9.

32. Rofagha S, Bhisitkul RB, Boyer DS, Sadda SR, Zhang K, Group S-US. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). Ophthalmology. 2013;120(11):2292-9.

33. Westborg I, Granstam E, Rosso A, Albrecht S, Karlsson N, Lövestam-Adrian M. Treatment for neovascular age-related macular degeneration in Sweden: outcomes at seven years in the Swedish Macula Register. Acta Ophthalmol. 2017;95(8):787-95.

34. Bhisitkul RB, Desai SJ, Boyer DS, Sadda SR, Zhang K. Fellow Eye Comparisons for 7-Year Outcomes in Ranibizumab-Treated AMD Subjects from ANCHOR, MARINA, and HORIZON (SEVEN-UP Study). Ophthalmology. 2016;123(6):1269-77.

35. Adrean SD, Chaili S, Ramkumar H, Pirouz A, Grant S. Consistent Long-Term Therapy of Neovascular Age-Related Macular Degeneration Managed by 50 or More Anti-VEGF Injections Using a Treat-Extend-Stop Protocol. Ophthalmology. 2018;125(7):1047-53.

36. Wykoff CC, Ou WC, Croft DE, Payne JF, Brown DM, Clark WL, et al. Neovascular age-related macular degeneration management in the third year: final results from the TREX-AMD randomised trial. Br J Ophthalmol. 2018;102(4):460-4.

37. Abdelfattah NS, Al-Sheikh M, Pitetta S, Mousa A, Sadda SR, Wykoff CC, et al. Macular Atrophy in Neovascular Age-Related Macular Degeneration with Monthly versus Treat-and-Extend Ranibizumab: Findings from the TREX-AMD Trial. Ophthalmology. 2017;124(2):215-23.

38. Rufai SR, Almuhtaseb H, Paul RM, Stuart BL, Kendrick T, Lee H, et al. A systematic review to assess the 'treat-and-extend' dosing regimen for neovascular age-related macular degeneration using ranibizumab. Eye (Lond). 2017;31(9):1337-44.

39. Dugel PU, Jaffe GJ, Sallstig P, Warburton J, Weichselberger A, Wieland M, et al. Brolucizumab Versus Aflibercept in Participants with Neovascular Age-Related Macular Degeneration: A Randomized Trial. Ophthalmology. 2017;124(9):1296-304.

40. Elman MJ, Ayala A, Bressler NM, Browning D, Flaxel CJ, Glassman AR, Jampol LM, Stone TW; Diabetic Retinopathy Clinical Research Network. Intravitreal Ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results.Ophthalmology. 2015 Feb;122(2):375-81.

41. Sun JK[1], Wang PW[2], Taylor S[2], Haskova Z[2] Durability of Diabetic Retinopathy Improvement with As-Needed Ranibizumab: Open-Label Extension of RIDE and RISE Studies. Ophthalmology. 2019 May;126(5):712-720.

42. Age-related macular degeneration NICE guideline [NG82] Published date: January 2018

43. Evidence-based recommendations on ranibizumab (Lucentis) for treating diabetic macular oedema in adults. NICE Technology appraisal guidance [TA274] Published date: 27 February 2013