Additional Considerations to Help Manage the Anti-VEGF Injection Burden during the COVID-19 Pandemic

Prepared for The Association of Canadian University Professors of Ophthalmology by:

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As the COVID-19 virus quickly becomes the public health crisis of our generation and out-patient clinics are significantly down-booked in hopes of reducing disease transmission to the vulnerable, ophthalmologists are left with the challenge of significantly reducing the use of anti-VEGF drugs where the preponderance of data suggests that for best visual outcomes we need to be treating patients more often not less.

The problem is that diabetic macular edema (DME), neovascular age-related macular degeneration (nAMD), and retinal vein occlusion with CME (RVO-CME) patient populations are older, often with significant co-morbidities - exactly the population most likely to require hospitalization, utilize intensive care unit (ICU) resources, or die should they become infected with COVID-19.

Suddenly for ophthalmologists, the overall health of our patients, office staff, and ourselves, is thrust to the fore, against our usual goals of saving vision and reducing ocular morbidity. Yet the question remains, at this time how can we best preserve visual function and, above all, reduce mortality? For some patients, visual disability may result from a reduction in number of treatments, but for others, this is not necessarily the case. What is certain is that the way we previously assessed, followed, and treated retinal diseases is no longer the safest approach to patient, provider and community during the COVID-19 crisis.

Changes in clinic processes are a necessary first step. Physicians should review injection patients' charts to see if visits can be delayed or treatment extended based on history alone - before bringing the patient to clinic. Patients should only be seen if it is absolutely necessary and then, to ensure our offices are safe for everyone: pre-screen patients for COVID-19 symptoms, space out appointments, rigorously clean examination and waiting rooms, constantly maintain physical distance for all, and practice meticulous hand-hygiene in addition

to other recommendations in the *COS and ACUPO Guidelines for Ophthalmic Care during COVID-19 Pandemic* from March 20, 2020. The number of patient visits in ophthalmology practices must be severely reduced to maintain these critical safety practices; however, treatments must still be maintained for those at significant risk of vision loss who are safe to bring to clinic; offices need to remain open so that the remaining treatment load is shared amongst as many injecting ophthalmologists as possible.

The Canadian Retina Society (CRS) brought forward very helpful recommendations on March 19, 2020 entitled *Canadian Retina Society (CRS) Position Statement on Intravitreal Injections and the Management of Retinal Diseases during the COVID-19 Crisis*. When using anti-VEGF drugs they "suggest consideration of extending intervals beyond what we have accepted as the maximal limits in the past.". They also advise "...clear and evidence-based decisions on optimal treatment algorithms.".

The Association of Canadian University Professors of Ophthalmology (ACUPO) seeks to expand on these foundational statements with the goal of minimizing the anti-VEGF treatment burden while mitigating the risk of loss of life and vision. What follows are evidence-based recommendations that, as always, do not replace appropriate clinical judgement; clinicians will need to consider the specifics of each patient's unique ocular and systemic health status and provide care that is in the patient's interest.

Recommendations are underlined, followed by supporting evidence.

1. **Teleophthalmology/Telemedicine**
    a. <u>Consider using phone calls, on-line resources, and teleophthalmology to triage patients.</u>
        i. Direct physician to patient phone calls are now being reimbursed in most jurisdictions and can be very useful for assessing subjective changes in vision and reassuring patients who are having their appointments delayed and/or treatment intervals lengthened without a clinic visit.
        ii. Numerous on-line resources are available for Amsler grid, visual acuity, colour vision, and field testing. While not ideal, meaningful changes in visual function can be picked up with these less specific testing modalities.
        iii. A low volume photography setting is likely safer than even a down-booked clinic. If treatment is needed, a short injection visit can then be arranged.
2. **Diabetic retinopathy**
    a. <u>Optimize systemic risk factors with a particular focus on patients with type 1 diabetes or type 2 diabetes on insulin treatment.</u>
        i. Only about 13% of Canadian patients with diabetes meet National targets for hemoglobin A1C, lipid levels, and blood pressures.[1] This is an ideal time to have patients re-engage with endocrine and family medicine

physicians to collaboratively use telemedicine or web-based approaches to minimize systemic retinopathy risk factors.

ii. By now, ophthalmologists should have significantly limited the number of daily injection visits that are conducted in their practices. For DME it is prudent to focus on patients with type 1 diabetes or type 2 diabetes being treated with insulin. The risk of blindness from DME in type 2 patients on oral agents is approximately 1/4 the risk for these other two groups. This directed approach, focusing on higher risk patients, will improve the overall therapeutic efficacy of anti-VEGF use.[2,3]

b. Initiation of anti-VEGF treatments can be delayed between 6 and 24 months - depending on the baseline visual acuity.

i. Don't treat DME immediately in the absence of vision loss (vision ≥ 20/25). *Protocol V* has shown that treatment can wait for patients with DME and good vision for 2 years without risk to visual acuity.[4]

ii. Anti-VEGF treatment for centre-involving DME (vision 20/30 to 20/200) does not have to be started immediately. While waiting 12 months to start injections is probably not ideal, a 6-9 month delay should not result in permanent vision loss. Looking specifically at cross-over studies where anti-VEGF therapy was deferred in one study arm, there is evidence that postponing injections is not unreasonable. The *RESTORE Study* delayed anti-VEGF treatment for one year in one study arm (allowing laser ≥ 3 months apart, for an average of 2 laser treatments in year one).[5] Anti-VEGF therapy was subsequently started, and this group regained equivalent visions by the end of year 2 that were maintained through year 3 (compared to those treated with 3 baseline injections and PRN dosing - for an average of 7 injections in year 1).[6] The *READ-2 Study* also showed complete visual recovery in its laser arm (also ≥ 3 monthly) where anti-VEGF therapy was delayed for 6 months.[7] The *RIDE and RISE Studies* allowed anti-VEGF treatment in one arm after 2 years of rescue laser. In these latter studies, visions did not recover to the same level as the anti-VEGF groups by the end of year 3, but did still improve.[8]

c. Use a Treat and Extend (T&E) approach and extend aggressively after year 2.

i. The *TREX-DME Study* compared monthly dosing to T&E and to T&E with laser. Seven fewer injections in the T&E with laser group, and 6 fewer injections in the T&E group were needed to obtain the same visual outcomes at the end of year 2.[9]

ii. In the DRCR.net *Protocol T*, after 2 years of treatment, patients tended to need significantly fewer treatments, such that > 50% of patients received < 5 injections from year 3 through year 5.[10] For almost all patients, monthly injections were not needed to maintain vision after year 2.

d. Consider how drug choice can reduce the need for follow-up visits and injections.

i. Aflibercept administered every 2 months has similar 3 year visual results compared to monthly treatment - as per the *VIVID and VISTA Studies*.[11,12]

Therefore, if Aflibercept is available, after loading doses, move immediately to at least a bimonthly interval.

ii. If possible, avoid the use of steroids as monitoring for pressure spikes likely will require extra office visits.

e. Treat proliferative disease with PRP.

i. Pan-retinal photocoagulation for high-risk proliferative disease without DME requires significantly fewer visits to stabilize the retinal pathology than anti-VEGF alone. In *Protocol S*, full PRP was administered in 2 sessions whereas, on average, 11 anti-VEGF injections were needed to control neovascularization over the 2 year study period.[13] Visual acuities were similar between groups at 2 and 5 years, with more advanced field changes in the PRP group through year 2, but field changes were equivalent between years 3 and 5.[14]

3. Neovascular AMD

a. Loading doses 2 and 3 do not require imaging; therefore, these injections can be performed in very short, treatment-only office visits.

b. Use a Treat and Extend (T&E) approach, tolerate modest residual sub-retinal fluid when extending, and consider extending by 4 week intervals.

i. The *MARINA and ANCHOR Studies* (monthly Ranibizumab treatments x 2 years) set the visual acuity bar for anti-VEGF treatment in nAMD (7-11 letter gain in year 1).[15,16] In the PrONTO study, PRN dosing was used after these three loading injections, and patients also did very well, with an average of only 5.6 injections in year one.[17] Given current COVID-19 concerns, the problem with monthly or PRN dosing is the obvious appointment burden. Hence, Treat and Extend (T&E) approaches are more appropriate at this time and are supported the data from trials such as the LUCAS Study[18] and the CANTREAT Study. The Lucas Study showed an 8 letter improvement at year one, and 7 letters at year two for both Bevacizumab and Ranibizumab - requiring 18 and 16 injections over 2 years, respectively. The CANTREAT Study[19,20] which compared a Ranibizumab T&E protocol to monthly injections found statistically equivalent visions at year 2 (+12.6 and +14.1 letters for the monthly injection and T&E groups, respectively), with 2 fewer injections in year one and 6 fewer injections by the end of year two with the T&E protocol.

ii. In the *VIEW Study*, after 3 injections of Aflibercept, approximately 80% of patients had no persistent leakage.[21] With 3 injections of ranibizumab, about 70% of patients had no leakage. Therefore, most patients should be dry after 3 loading doses and an earlier and more aggressive extension of treatment interval may make sense. The *ALTAIR Study* showed that extending by 4-weeks at a time (as compared to the usual 2 week interval) did not adversely affect visual acuities through the 2 year study period. Also, many patients were able to be maintained on one dose every 4 months.[22]

iii. The *FLUID Study* suggests that small amounts of subretinal fluid in the absence of intraretinal edema can be tolerated in nAMD patients.[23] Patients treated with a ranibizumab T&E protocol that tolerated some sub-retinal fluid (SRF) achieved final visions (with fewer injections) that were comparable to those whose treatment goal was to resolve all SRF. Significantly more participants in the SRF-tolerated group extended to and maintained 12-week treatment intervals (29.6%) than the intensive treatment group (15.0%).

c. <u>If not using Treat and Extend, there are other approaches that can reduce injection visits.</u>
   i. The *PIER Study* (3 loading doses then quarterly Ranibizumab) didn't have visual results that approached the pivotal trials, but did improve the acuity by >4 letters at year 1. This approach is considerably better than no treatment and could be considered for patients at very high risk for complications from COVID-19.[24]
   ii. In the *VIEW Study*, for Aflibercept over 2 years, eight-weekly dosing was visually equivalent to monthly treatment intervals for Ranibizumab or Aflibercept.[21] If available, Aflibercept is a good choice if treatment as per a clinical trial is considered - though the use of such an approach at this time would be highly questionable.

d. <u>For polypoidal choroidal vasculopathy, use anti-VEGF in conjunction with PDT.</u>
   i. The *Everest Study* showed using combined therapy, we can reduce injections over the first year of treatment from 7 to 4.[25]

4. Retinal Vein Occlusion with CME

a. <u>Anti-VEGF treatment can be delayed for up to 3 months from disease onset and can be administered with a T&E approach.</u>
   i. The *LEAVO Study* confirmed that CME from CRVO can be managed with a Treat and Extend treatment protocol that allows the injection interval to extend out to 8 weeks. Also, Aflibercept use led to 2 fewer injections compared to Ranibizumab over the 2-year study period (12 vs. 10, 95% CI -2.9 to -0.8).[26]
   ii. Most RVO studies allowed recruitment of patients for 3 months after disease onset, hence immediate treatment is probably not essential for good visual outcomes.

5. <u>Stopping criteria for anti-VEGF therapies for each of these diseases should be carefully considered at each visit.</u>
   a. Continued therapy in the setting of advanced, irreversible macular pathology and very poor vision should be avoided.

Given the abruptly changed environment in which we now practice, the data presented above offer evidence-based approaches for the management of patients receiving anti-VEGF therapy in a way that minimizes ocular morbidity, while reducing injection volumes and the related risk of patients and health care workers contracting COVID-19. An additional benefit is an expected

reduction in the number of injection-related complications that could further strain our health care system and increase patient exposure to the hospital or clinic setting.

Figure 1: DME approach to reducing injection visits:

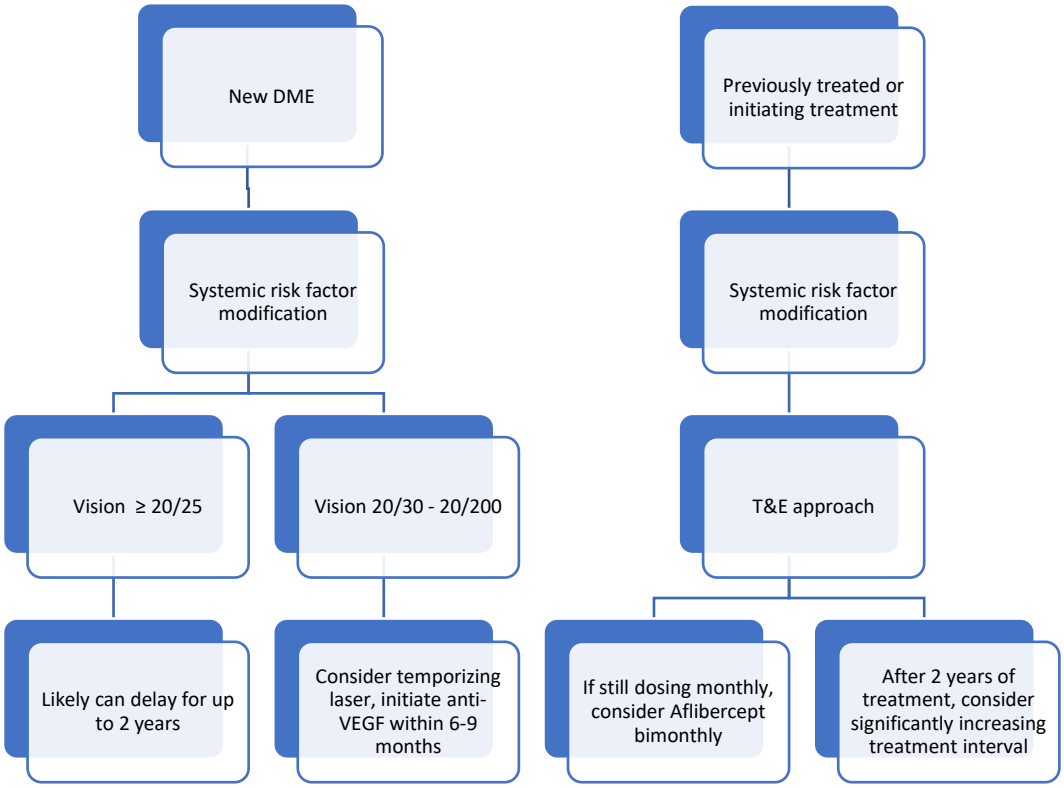

Figure 2: Neovascular AMD approach to reducing injection visits:

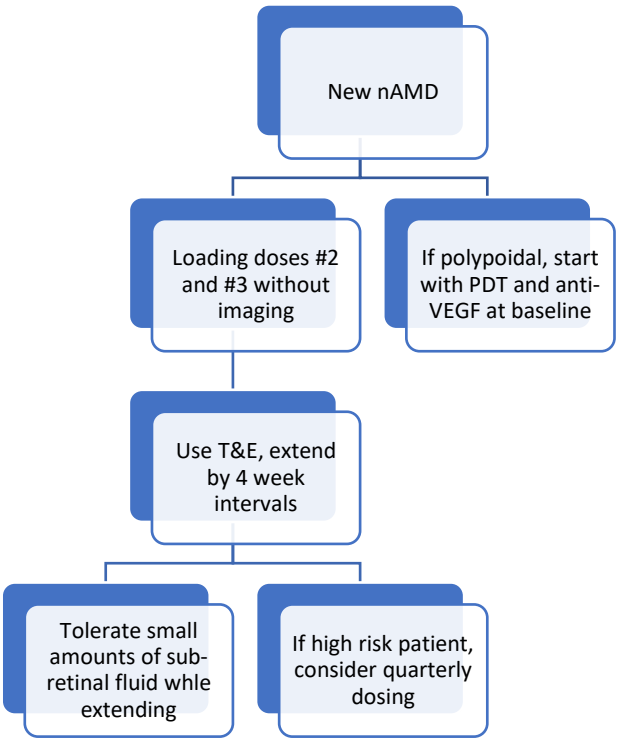

Table 1: Summary of Included Studies:
(Rani = Ranibizumab; Beva = Bevacizumab; Aflib = Aflibercept; PVDT = Photodynamic Therapy with Verteporphin)

Study	N	Intervention	Design	Outcome
Diabetic Macular Edema and Proliferative Diabetic Retinopathy				
Baker et al. 2019 (JAMA)[4] DRCR.net Protocol V	702	Aflib vs laser vs observation	RCT	5 letter visual acuity decrease from baseline at 2 years and ADEs
RESTORE Extension Study (2014)[5]	240	Rani PRN vs laser vs both	RCT	Mean change in BCVA and incidence of ocular and non-ocular ARs
RESTORE Extension Study (2014)[6]	240	Ranibizumab vs laser vs both	RCT	Change in BCVA and incidence of ocular and non-ocular AEs over 3 years
READ-2[7]	126	Rani at different intervals vs focal/grid laser photocoagulation or both	RCT	Mean change in BCVA at month 24
RISE and RIDE[8]	759	Rani 0.3 vs Rani 0.5 vs sham injection	RCT	BCVA at month 24
TREX-DME[9]	150	Rani monthly vs Rani T&E vs Rani T&E + Laser	RCT	Mean change in BCVA at 1 year, number of injections
DRCR.net Protocol T Extension Study[10]	317	Aflib vs Beva vs Rani	RCT	Anti-VEGF treatment, letter score, and central subfield thickness
VISTA and VIVID 2014[11]	872	Aflib q4, Aflib q8, vs laser control	RCT	BCVA at week 52
VISTA and VIVID 2016[12]	872 e	Aflib q4, Aflib q8, vs laser control	RCT	BCVA at week 148
DRCR.net Protocol S[13] & Maguire et al. 2020 (JAMA Ophthalmology)[14]	234	Rani vs photocoagulation	Post Hoc analysis of RCT (observational)	Mean change in total point score on VF testing (30-2 and 60-4 patterns)
Neovascular Age-related Macular Degeneration				
MARINA[15]	716	Rani vs Sham	RCT	Mean increase in BCVA
ANCHOR[16]	423	Rani vs Sham	RCT	Mean increase in BCVA
PRONTO[17]	40	Rani: 3 consecutive injections then PRN	Observational Prospective Cohort	
LUCAS[18]	441	Rani vs Beva Q 4 weeks until inactive disease then extended 2-12 weeks	Non inferiority RCT	Mean change in BCVA in two years
CANTREAT[19,20]	580	Rani monthly vs T&E	RCT	BCVA change at 52 weeks
VIEW 1,2[21]	2,419	Aflib at different intervals vs Rani	RCT	Maintaining vision (<15 letters) at 52 weeks

ALTAIR[22]	123	3 x doses of Aflib then randomized to treat an extent	RCT	BCVA at 52 and 96 weeks BCVA
FLUID[23]	349	Rani intensive, Rani relaxed	RCT	BCVA change at 100 weeks
PIER[24]	184	Rani monthly x 3 months then quarterly vs Sham	RCT	BCVA at 52 weeks
EVEREST[25]	322	Rani+PVDT, Rani, Sham	RCT	BCVA change at 52 weeks
Central Retinal Vein Occlusion with CME				
LEAVO[26]	463	Rani vs Aflib vs Beva		BCVA change at 100 weeks

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