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Evaluating the Comparative Efficacy and Safety of Anti-VEGF Agents in Treating DME: A Canadian Perspective on the Protocol T Trial

Analysis of the recent DCRC.net trial in the context of Canadian daily practice and management of diabetic macular edema

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Over the past decade, anti-vascular endothelial growth factor (VEGF) therapy has become the mainstay of treatment for VEGF-mediated retinal disease, including age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO). Until recently, ranibizumab was the only Health Canada-approved intravitreal anti-VEGF agent, and treating physicians were faced with a dilemma over use of this approved therapy versus the more cost effective but off-label bevacizumab. The choice was further influenced by the constraints of each province's unique formulary requirements and other access-related challenges. Recent Health Canada approval of aflibercept has complicated the therapeutic decision-making process, especially given the possibility that aflibercept, with its unique mechanism of action, may be associated with longer treatment intervals in select patients. Duration of drug action is an issue of particular importance because the high frequency of visits for intravitreal injections associated with current treatment paradigms present a significant treatment burden for patients, caregivers and their treating physicians. To overcome this burden, the majority of retina specialists in Canada currently rely on individualized treatment strategies by applying either a treat-and-extend or as-needed approach. Due to the lack of head-to-head comparative efficacy trials comparing anti-VEGF agents in DME, however, many retina specialists questioned whether the theoretical benefits of aflibercept would translate into a true clinical efficacy advantage. To that end, recently published results from the Protocol T trial,[1] comparing intravitreal aflibercept, bevacizumab, and ranibizumab for the treatment of DME, generated a great deal of interest. This issue of *Ophthalmology Scientific Update* provides an overview of the Protocol T data in the context of Canadian daily practice and management of DME.

The Role of Vascular Endothelial Growth Factor (VEGF) in the Pathogenesis of Diabetic Macular Edema (DME): Rationale for Anti-VEGF Therapy

Intraocular neovascularization occurs in numerous ischemic retinal disorders and VEGF is a key component in their pathogenesis.[2] This vasoactive cytokine stimulates neovascularization and increases retinal permeability, leading to extracellular fluid accumulation and macular edema.[2,3] Macular edema is the main cause of vision loss in diabetic patients and aqueous VEGF concentrations in DME eyes were found to be elevated nearly 5-fold compared to controls,[4] providing a rationale for the use of intravitreal anti-VEGF therapy in the treatment of DME.[5,6] In addition, recent evidence demonstrated that anti-VEGF treatment reduces the severity of diabetic retinopathy (DR) on the Early Treatment Diabetic Retinopathy Study (ETDRS) DR severity scale, which points to an ability to the possibility of disease modification and altering its natural history.[7]

It is also noteworthy that although VEGF-mediated retinal diseases such as age-related macular degeneration (AMD) and DME display some overlapping phenotypic characteristics the underlying mechanisms and pathophysiology of these disease states are different. While the clinical and histopathological features of AMD involve pigmentary disturbances, presence of drusen, thickening of Bruch membrane, and basal laminar deposits,[8] the pathophysiology of DME is driven by chronic elevation of serum glucose levels that leads to pericyte loss, capillary

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damage, and microaneurysm formation in the retina. Leakage from these microaneurysms can result in vision impairment when the accumulation of fluid involves the centre of the fovea. Furthermore, while AMD patents are more likely to require ongoing anti-VEGF treatments life-long to maintain vision gains,[9] that may not be the case for DME.[10-14] Several trials demonstrated that improvements in visual acuity (VA) achieved with frequent anti-VEGF therapy during the first year of treatment can be maintained with fewer injections throughout the second and third years.[11-14] In the RISE and RIDE trials VA gains achieved after 3 years of monthly ranibizumab injections were maintained with a PRN dosing schedule. The mean number of injections over the following 12 months was 3.8 in patients who required further treatment. Furthermore, approximately 25% of patients did not require further anti-VEGF therapy.[10]

As DR and DME are consequences of microvascular complications of impaired glucose metabolism, their management also depends on the systemic control of diabetes. DME patients often require prompt initiation of anti-VEGF therapy at the outset with a decremental need for further treatment in a large majority of patients with longer-term follow-up.[10]

Clinical Trials of Anti-VEGF Agents

Table 1 provides an overview of Health Canada-approved indications for anti-VEGF therapies for the treatment of DME.[15,16]

In Canada, approval of ranibizumab for the treatment of DME is based on the RESOLVE and RESTORE trials.[13,15,17] The RESOLVE study[17] randomized 151 patients to intravitreal ranibizumab (0.3 or 0.5 mg; n=51 each) or sham (n=49). At the 1-year endpoint, patients receiving ranibizumab had improved significantly, gaining an average of 10.3 letters (pooled data), while patients treated with laser alone lost an average of 1.4 letters. In the RESTORE trial,[13] ranibizumab (0.5 mg, 3 monthly injections followed by PRN dosing) as monotherapy or in combination with laser provided superior gain in VA over laser alone in patients with visual impairment due to DME.[13] Based on these results, Health Canada approved ranibizumab for the treatment of DME at the dose of 0.5 mg. In the United States (US), approval of ranibizumab for the treatment of DME is based on the RISE and RIDE trials.[18,19] In these trials, patients received either monthly injections of ranibizumab (0.3 mg or 0.5 mg) or sham at each monthly visit for 2 years. Monthly injections of ranibizumab were shown to be significantly superior to sham injections in improving best-corrected VA (BCVA) over 24 months and required significantly fewer macular laser procedures.[18] After 24 months, sham patients crossed over to ranibizumab 0.5 mg and all patients continued with monthly treatments for another year (a total 36 months of monthly injections).[19] All patients who completed month 36 of the core studies were eligible to enroll in the open-label extension (OLE), during which they received ranibizumab (0.5 mg) on a PRN basis.[10] Figure 1 shows changes from the baseline in BCVA for 3 treatment groups. As shown, while both doses of ranibizumab were effective in improving vision, higher visual benefit was achieved in patients receiving ranibizumab from the study outset compared to sham patients who were switched to ranibizumab after 24 months. This supports the importance of early institution of anti-VEGF therapy in patients with DME.[10] In regard to systemic safety, at month 36 more deaths (6.4% versus 4.4%) and strokes (4.8% versus 2.0%) occurred in patients treated with 0.5 mg compared to those treated with 0.3 mg.[19] Based on this observation, the 0.3-mg dose – ie, the lowest effective dose – was submitted and subsequently approved by the Food and Drug Administration (FDA) for the treatment of DME; in all other countries, 0.5 mg is the approved DME dose. It is interesting to note that after 4 years of treatment the rates of cerebrovascular events and deaths were numerically higher in the patients originally randomized to the 0.3-mg dose versus the 0.5-mg dose (deaths: 5.8% versus 3.7%; events in the central nervous system: 3.5% versus 1.8%).

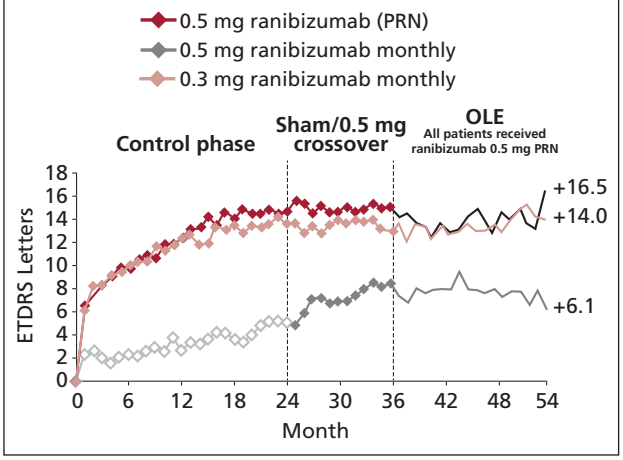
The approval of aflibercept in Canada and the US is based on the VIVID and VISTA trials that demonstrated superiority of 2 mg aflibercept (5 monthly loading doses, then dosing of drug administered every 4 or every 8 weeks [q4w and q8w]) versus laser in the treatment of DME.[20,21] At week 100, BCVA was improved from baseline by means of 11.5 and 11.1 letters in the aflibercept q4w and q8w arms, respectively, and by 0.9 letters in the laser-treated control group.[21] Aflibercept was also superior to laser in preventing significant vision loss. At week 100, the proportion of eyes losing ≥15 letters from baseline BCVA was significantly lower in the aflibercept q4w and q8w groups compared

Table 1: Anti-vascular endothelial growth factor (VEGF) therapies: Health Canada-approved indications for diabetic macular edema (DME)

Anti-VEGF therapy	Recommended dose	Corresponding injection volume	Dosing interval
Ranibizumab[15]	0.5 mg	0.05 mL	Administered monthly and continued until maximum VA is achieved,[a] after which patients can receive PRN treatment with monthly assessment If a loss of VA is detected, treatment is resumed with monthly injections
Aflibercept[16]	2 mg	0.05 mL	Administered monthly for the first 5 consecutive doses, followed by 1 injection every 2 months[b]

[a]Maximum visual acuity (VA) is confirmed by stable VA for 3 consecutive monthly assessments; [b]aflibercept dosed as frequently as 2 mg every month showed similar efficacy to aflibercept dosed 2 mg once every 2 months in the DME clinical trials.

Figure 1: RISE and RIDE OLE phase: pooled mean BCVA change from baseline[10]



OLE = open-label extension; BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study

with the control (3.2% and 0.7% versus 9.7%).[21] Gains of ≥15 letters at week 100 were seen in 38.3%, 33.1%, and 13.9% in the q4w, q8w, and laser groups, respectively.[22]

Protocol T

Trial design

Protocol T was a multicentre (89 clinical sites in the US), randomized, clinical trial sponsored by the National Institute of Health and conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net).[1] The objective was to compare intravitreal aflibercept, bevacizumab, and ranibizumab for the treatment of DME involving the centre of the macula and causing vision impairment. The study randomized 660 patients (mean age, 61±10 years) to aflibercept (2.0 mg; n=224), bevacizumab (1.25 mg; n=218), or ranibizumab (0.3 mg; n=218). Patients were treated q4w using the treatment algorithm validated in the DRCR Protocol I study.[23] Injection of drug was given at each visit unless VA was 20/20 with a central subfield thickness (CST) <250 µm on 2 consecutive visits or, if beyond 24 weeks of treatment, there was no change in either VA or CST on optical coherence tomography (OCT) after 2 consecutive injections. Treatment was reinstated if there was a significant change in VA letter score (≥5 letters) or a 10% change in CST thickness. The primary outcome was the mean change in VA at 1 year. Beyond 24 weeks, laser photocoagulation was initiated in patients with persistent DME.

The major inclusion criteria comprised VA (~Snellen equivalent) between 20/32 and 20/320 and DME-related retinal thickening involving the centre of the macula, confirmed by both OCT and physical examination. At baseline about 50% of participants has VA of 20/32 to 20/40, and 50% had VA of 20/50 or worse. Notably, the mean baseline VA levels in the Protocol T trial (69 letters for aflibercept and bevacizumab and 68 for ranibizumab; Table 2) are higher compared to VA scores in other DME trials.[13,17,18,20] The median hemoglobin (Hb) A_{1C} levels in the Protocol T trial were 7.6%–7.8%, which is similar to HbA_{1C} levels in other DME clinical trials[13,18,20] but higher than what is typically encountered in the routine clinical practice.

Efficacy outcomes

At 1 year, the mean improvement in the VA letter score was greatest with aflibercept (13.3 letters) compared to bevacizumab (9.7 letters) or ranibizumab (11.2 letters) (P<0.001 for aflibercept versus bevacizumab and P=0.03 for aflibercept versus ranibizumab; Table 3). Although statistically significant, the clinical significance of a 2-letter mean VA gain between groups is difficult to gauge, especially when consideration is given to the 1-letter difference in baseline VA between ranibizumab and the other treatment groups (interaction, P<0.001).[1] Impact of baseline VA on visual outcomes was determined *a priori* via prespecified subgroup analysis comparing outcomes in subgroups with VA better than 20/40 at baseline to those with vision of 20/50 or worse. For patients with an initial VA of 20/32 to 20/40 (50% of the cohort), the mean improvement from baseline was 8.0±7.6 with aflibercept, 7.5±7.4 with bevacizumab, and 8.3±6.8 with ranibizumab. These differences were not statistically significant. When the initial VA was 20/50 or worse, the mean improvement was 18.9±11.5 with aflibercept, 11.8±12.0 with bevacizumab, and 14.2±10.6 with ranibizumab (P<0.001 for aflibercept versus bevacizumab, P=0.003 for aflibercept versus ranibizumab, and P=0.21 for ranibizumab versus bevacizumab).

At the 1-year visit, the CST decreased, on average, by 169±138 µm with aflibercept, 101±121 m with bevacizumab, and 147±134 µm with ranibizumab (P=0.036 for aflibercept versus ranibizumab, and P<0.001 for both aflibercept and ranibizumab versus bevacizumab). Again, the relative treatment effect on CST varied according to initial VA (Table 4). Aflibercept and ranibizumab reduced retinal thickness more than bevacizumab, but the anatomical benefit translated into a VA benefit only in eyes with a baseline VA of 20/50 or worse. The retinal volume changes were similar for ranibizumab and aflibercept (-1.7 mm^3) versus -1.0 mm^3 for bevacizumab. This suggests that bevacizumab might be less effective in drying retina, which has also been indicated by the findings from the CATT[24] and IVAN[25] trials in patients with AMD.

Between 24 and 48 weeks, laser was administered at least once in 76 of 208 aflibercept-treated eyes (37%), 115 of 206 bevacizumab-treated eyes (56%), and 95 of 206 ranibizumab-treated eyes (46%) (P<0.0001 for aflibercept versus bevacizumab; P=0.058 for aflibercept versus ranibizumab; P=0.061 for bevacizumab versus ranibizumab).

Table 2: Protocol T: Baseline VA letter scores[1]

VA letter score	Aflibercept	Ranibizumab	Bevacizumab
Overall	69	68	69
Letter score <69	56.2	56.5	56.6
Letter score 69–78	73.5	73.4	72.8

Table 3: Protocol T: 1-year improvement in VA letter scores[1]

Mean change in VA at 1 year	Aflibercept	Ranibizumab	Bevacizumab	*P*
Overall	+13.3	+11.2	+9.7	Aflibercept vs ranibizumab: *P*=0.034 Aflibercept vs bevacizumab: *P*<0.001 Ranibizumab vs bevacizumab: *P*=0.12
Letter score <69	+18.9	+14.2	+11.8	Aflibercept vs ranibizumab: *P*=0.003 Aflibercept vs bevacizumab: *P*<0.001 Ranibizumab vs bevacizumab: *P*=0.21
Letter score 69–78	+8.0	+8.3	+7.5	*P*=0.69 for all comparisons

Safety outcomes

There were no significant differences in safety observed among the agents. Rates of ocular adverse events, including rates of endophthalmitis, were not significantly different between groups. Rates of Antiplatelet Trialists' Collaboration (APTC) events,[26] typically associated with anti-VEGF use for intravenous therapy of metastatic colorectal cancer,[27] were not significantly different between groups. They occurred in 3%, 4%, and 5% of patients treated with aflibercept, bevacizumab, and ranibizumab, respectively (*P*=0.72; Table 5). It is important to note that the sample sizes used in Protocol T were not adequately powered for detection of safety differences.

In a *post hoc* analysis, there were more cardiovascular events in patients treated with ranibizumab (37 patients, 17%) than in those receiving aflibercept (20 patients, 9%) or bevacizumab (19 patients, 9%; *P*=0.01). Given the absence of clinical data suggesting a difference in cardiovascular safety in other DME trials and in comparative trials of these drugs in AMD, the authors concluded that this finding may have been due to chance.[1]

Interpretation of the Protocol T Data

When comparing the vision outcomes and OCT data generated from Protocol T, particularly in the subgroup of patients of with worse VA at baseline, it would be tempting to conclude that aflibercept is the more effective anti-VEGF agent in the treatment of centre-involved DME. Protocol T results require more careful consideration and analysis before any meaningful conclusions can be made with regards to impact on clinical practice. To date, all indirect comparisons of vision outcomes using anti-VEGF agents in other clinical trials for both DME and AMD have shown evidence of comparable efficacy.

With regard to treatment of DME in Canada specifically, the importance of the utilization of the 0.3-mg FDA-approved dose of ranibizumab in Protocol T (instead of the 0.5-mg dose approved by Health Canada) cannot be overlooked. The 0.3-mg dose validated in the RISE/RIDE studies used a monthly dosing protocol where drug was injected monthly for 36 months consecutively. The 0.3-mg dose, used on a PRN basis, has not been previously validated as equivalent to 0.5 mg PRN in the treatment of DME. Although the 0.3-mg PRN dose was used in one arm of the RESOLVE trial, only pooled data (0.5 mg and 0.3 mg) from this trial are reported.[17] Furthermore, most clinical trials using different doses of ranibizumab have demonstrated evidence of a dose-response curve, with better outcomes with the 0.5-mg dose as compared to 0.3 mg.[28-31] Thus, it is possible that the 0.3-mg PRN dose is not the ideal comparison to 2 mg of aflibercept.

Accordingly, an analysis of comparative efficacy of the 0.3-mg to the 0.5-mg dose of ranibizumab from other clinical trials completed to date becomes relevant. In the RIDE trial, with monthly dosing of ranibizumab, there was a

Table 4: Protocol T: Mean change in central subfield thickness[1]

CST	Aflibercept	Ranibizumab	Bevacizumab	*P*
Overall Baseline (µm) Change (µm)	 412 -169	 407 -147	 414 -101	Aflibercept vs ranibizumab: *P*=0.036 Aflibercept vs bevacizumab: *P*<0.001 Ranibizumab vs bevacizumab: *P*<0.001
Letter score <69 Baseline (µm) Change (µm)	 452 -210	 431 -176	 476 -135	Aflibercept vs ranibizumab: *P*=0.22 Aflibercept vs bevacizumab: *P*<0.001 Ranibizumab vs bevacizumab: *P*<0.001
Letter score 69–78 Baseline (µm) Change (µm)	 373 -129	 384 -119	 363 -67	Aflibercept vs ranibizumab: *P*=0.06 Aflibercept vs bevacizumab: *P*<0.001 Ranibizumab vs bevacizumab: *P*<0.001

Table 5: Protocol T: Vascular events[a] occurring at least once through first year of treatment[1]

Vascular event	Aflibercept	Bevacizumab	Ranibizumab	*P*
Nonfatal myocardial infarction	4 (2%)	1 (<0.5%)	3 (1%)	–
Nonfatal stroke	0	4 (2%)	4 (2%)	–
Death from potential vascular cause or unknown cause	2 (1%)	4 (2%)	3 (1%)	–
Any event	6 (3%)	9 (4%)	10 (5%)	0.56

[a]Vascular events were defined according to the criteria of the Antiplatelet Trialists' Collaboration[26]

higher percentage of patients in the 0.5 mg group who gained ≥3 lines of VA compared to those treated with 0.3 mg. In the subgroup of patients with worse VA at baseline, 69.5% of patients treated with the 0.5-mg dose of ranibizumab gained ≥15 letters.[19] This may be more comparable to the 67% figure of 3-line gainers in Protocol T for patients with baseline VA of ≤20/50 treated with 2 mg of aflibercept.[1] In addition, in the VIEW 1 and 2 trials, the visual outcomes with 0.5 mg ranibizumab were similar to those achieved with 2 mg aflibercept in neovascular AMD patients.[32] At 2 years the average gain in patients treated with ranibizumab was 7.9 letters versus 7.6 letters in those receiving aflibercept.

The addition of the laser may have also been a confounder. Patients with persistent centre-involved DME beyond 24 weeks were mandated to have laser. While the lower percentage of laser required in aflibercept-treated eyes might suggest evidence of better anatomical outcomes, the detrimental effect of laser on vision itself cannot be ignored. Given the 5-year results of DRCR protocol I suggesting better visual outcomes in the ranibizumab-treated patients with deferred versus prompt laser,[33] the possibility that the visual outcomes may have been negatively affected in the bevacizumab and ranibizumab treated patients must be considered.

Key Lessons from the Protocol T Trial

The Protocol T trial demonstrated that all 3 anti-VEGF agents are effective treatment options for patients with centre-involved DME. In patients with mild vision loss, all 3 available anti-VEGF agents appear equally effective after 1 year of treatment. In those with more significantly impaired vision (20/50 or worse), aflibercept appears to have better vision outcomes when compared to bevacizumab and a 0.3-mg dose of ranibizumab. At 1 year and regardless of baseline VA, bevacizumab was less effective than either aflibercept or ranibizumab in reducing fluid and macular edema. Although this did not translate into a clinically significant difference in mean vision gained at 1 year in the entire cohort, it is possible that a difference in efficacy may become more apparent with longer-term follow-up. Accordingly, 2-year results of the Protocol T may help to further delineate any differences in efficacy between the agents in the management of DME.

Conclusions in Relation to Canadian Practice

The benefit of a 2-mg dose of aflibercept in the management of DME, as demonstrated by the recent 1-year results of Protocol T, cannot be overlooked. Despite the fact that 0.3 mg is not the Health Canada-approved dose of ranibizumab, the contention that the 0.5-mg dose might compare more favourably when used on a PRN basis is speculative. Protocol T has conclusively demonstrated that baseline vision may be of critical importance in the decision-making process and has the potential to reinforce the necessity of the individualized treatment approach commonly adopted by Canadian retina specialists in the treatment of centre-involved DME. Protocol T results have also validated the benefits of both aflibercept and ranibizumab over bevacizumab as "drying" agents in the reduction of macular edema. This is of particular relevance to Canadian practice as evidenced by the inclusion of bevacizumab on some provincial formularies. At this time, access to drug and reimbursement-related challenges will likely continue, in the short term, to be the most relevant consideration to treating physicians and patients alike with regards to drug selection for treatment of DME.

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