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## Contemporary Management of Retinal Disease: Focus on Individualized Treatment Approaches

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With the continuous use of anti-vascular endothelial growth factor therapies in the management of retinal diseases – particularly wet age-related macular degeneration, diabetic macular edema, retinal vein occlusion, and myopic choroidal neovascularization – the importance of an individualized therapeutic approach is becoming increasingly recognized. Many initiatives have been implemented to identify prognostic factors that can help in guiding therapeutic approaches toward the most desirable outcomes. This issue of *Ophthalmology Scientific Update* summarizes presentations and other new data on the value and usefulness of various patient- and disease-related features that might serve as predictors of future outcomes as well as on the potential impact of this evidence on Canadian daily ophthalmology practice.

### Wet Age-Related Macular Degeneration (AMD): Baseline Characteristics as Predictors of Response to Anti-Vascular Endothelial Growth Factor (VEGF) Therapy

Several presentations discussed the association between visual acuity (VA) outcomes and anatomical (central retinal thickness [CRT]) and morphological (presence of retinal fluid, development of geographic atrophy) changes in the key AMD clinical trials. A subanalysis of 2-year CATT trial data (N=1185) indicated that eyes with subretinal fluid on optical coherence tomography (OCT) – 84% at baseline and at 2 years – had better mean VA than eyes with no fluid (70.9 versus 67.0 letters;  $P=0.006$ ).<sup>1</sup> On the other hand, the presence of intraretinal fluid worsened mean VA (59.9 versus 70.9 letters;

$P<0.0001$ ). Overall, 85% of CATT participants had fluid on OCT at baseline and at year 2. Abnormally thin retinas were associated with worse VA outcomes: 59.4 letters for eyes with retinal thickness  $\leq 120$   $\mu\text{m}$  versus 71.3 letters for 120–212  $\mu\text{m}$  and 70.3 letters for  $>212$   $\mu\text{m}$  ( $P<0.0001$ , Figure 1). In addition, greater choroidal neovascularization (CNV) lesion area ( $P<0.0001$ ) and greater subretinal tissue complex thickness ( $P=0.03$ ) were also associated with worse visual outcomes. Data from the VIEW 1 and 2 trials also indicated a significant association between suboptimal VA response and lesion size at baseline.<sup>2</sup> In the IVAN trial, individuals presenting with larger and more active lesions (presence of hemorrhage or classic CNV) had worse baseline visual function.<sup>3</sup>

The EXCITE investigators found no linear correlation between CRT and 12-month VA gain.<sup>4</sup> However, when patients with baseline CRT  $\geq 275$   $\mu\text{m}$  (n=179) were stratified according to retinal thickness at 12 months, VA gain was the highest (median 8 letters) for the intermediate (150–250  $\mu\text{m}$ ) stratum, compared with a median VA gain of 6 letters for patients with the thinnest retina ( $\leq 150$   $\mu\text{m}$ ) and 3 letters for the thickest retina ( $>300$   $\mu\text{m}$ ; Table 1). The authors concluded that CRT reduction with ranibizumab is associated with best corrected (BC) VA gain to a CRT threshold, below which additional reduction in retinal thickening does not convey additional BCVA gain.

### Diabetic Macular Edema (DME): Reducing the Visit Burden while Maintaining Visual Outcomes

The efficacy and safety of intravitreal ranibizumab in the management of DME have been demonstrated in several large, randomized clinical trials,<sup>5–9</sup> in which the frequency of treatment varied from monthly injections<sup>5</sup> to less frequent as-needed (prn)

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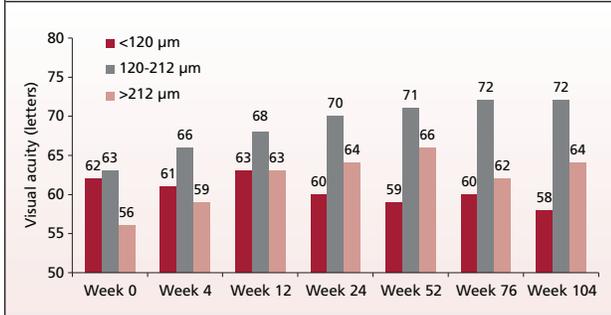
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**Figure 1: CATT:<sup>1</sup> relationship between retinal thickness and visual acuity (VA)**



regimens.<sup>6-9</sup> As frequent clinic visits present a significant burden on patients, treating clinicians, and the healthcare system, several therapeutic approaches that would ensure good visual outcomes with less frequent injections and monitoring have been explored.

Dr. Christian Prunte presented 24-month data from the RETAIN trial,<sup>10</sup> a single-masked Phase III study that evaluated efficacy and safety of ranibizumab (0.5 mg) in 2 treat-and-extend regimens versus prn. After initial stabilization of VA with monthly ranibizumab, 372 patients were randomized to treat-and-extend ranibizumab with (n=121) and without laser (n=128) or to prn ranibizumab (n=123). Laser was performed on day 1 and then prn based on Early Treatment of Diabetic Retinopathy Study (ETDRS) guidelines. In the treat-and-extend groups, treatment- and monitoring-free intervals were incrementally extended by 1 month (up to 3 months), and the prn group was monitored monthly. Mean changes in BCVA at 24 months demonstrated noninferiority of the treat-and-extend regimens to prn treatment: +8.3 ETDRS letters in patients receiving treat-and-extend ranibizumab plus laser, +6.5 letters with treat-and-extend ranibizumab monotherapy, and +8.1 letters with prn treatment. Treat-and-extend regimens reduced the number of patient visits by 40% and more than 70% of patients on the treat-and-extend regimen had a clinic visit-free interval of <sup>≥</sup>2 months.

Similarly, the prospective, open-label, single-arm, Phase IIIb RELIGHT study<sup>11</sup> (N=109 enrolled, 99 completed) supported the

**Table 1: EXCITE trial:<sup>4</sup> Relationship between CRT and VA gain in patients with baseline CRT  $\geq$ 275 μm**

CRT at Month 12 (μm)	n	Change from baseline to Month 12	
		Median BCVA (ETDRS letters)	Median CRT (μm)
≤150	22	+6	-214
150–200	48	+8	-172
201–250	55	+8	-125
251–300	32	+4	-76
>300	22	+3	-2

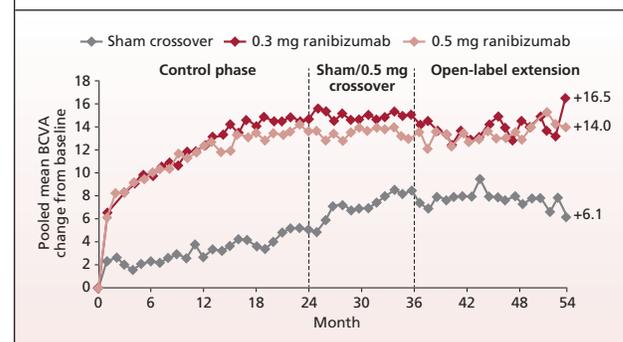
CRT = central retinal thickness; BCVA = best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study

feasibility of a bimonthly monitoring-guided treatment regimen. The proportion of individuals gaining  $\geq$ 10 and  $\geq$ 15 letters at Month 12 was 24.8% and 13.8%, respectively. By Month 18, 35% of patients gained  $\geq$ 10 and 19% gained  $\geq$ 15 letters. The mean numbers of injections (including 3 monthly loading doses) were 6.8 and 8.5 over 12 and 18 months, respectively. Moreover, a subgroup analysis of the RELIGHT trial suggested that patients with a shorter duration of DME (<12 months) achieved greater improvements in BCVA compared to patients with a longer duration.

The importance of early intervention was also noted in the RIDE and RISE trials,<sup>12</sup> where subjects switched from sham injections to ranibizumab after 2 years did not reach the same VA level as those on ranibizumab from trial onset. Avoiding the treatment delay is of particular importance in patients with subretinal fluid, severe edema, large cysts, and renal disease.<sup>13</sup> In Year 3 of RISE and RIDE, patients receiving sham for 2 years were eligible for crossover to monthly 0.5 mg ranibizumab. After Month 36, patients could receive open-label 0.5 mg ranibizumab regardless of prior randomization. According to the results of long-term open-label extension of these trials, about 25% of patients did not require further ranibizumab treatment to maintain VA and approximately 75% were able to maintain their VA with additional treatments (Figure 2). An average of 4.5 injections were administered over a mean 14.1 months follow-up in the open-label extension, with only 10% of patients requiring monthly injections.<sup>12</sup>

A *post hoc* analysis of the RESTORE study investigated participant baseline characteristics in an attempt to identify predictors of the high VA response ( $\geq$ 10 ETDRS letter gain at 12 months).<sup>14</sup> The mean number of injections in high VA responders was 6.9 and resulted in a mean VA gain of 15.1 letters, compared to 7.2 injections and 7.5 letters in the overall trial population. None of the evaluated baseline characteristics (VA, CRT, age, body mass index and hemoglobin A1c) predicted the frequency of treatment required for high VA response. However, the observation that 40% (32/81) of high VA responders required  $\leq$ 6 injections for a similar gain in VA (15.8 letters) during the first year of treatment supports an individualized therapeutic approach for the management of DME. Subanalysis of the RESTORE data by Gerendas et al<sup>15</sup> showed that active disease at baseline, particularly the presence of intraretinal cysts and subretinal fluid, is associated with

**Figure 2: Open-label extension of the RIDE and RISE trials indicating the need of earlier therapeutic intervention<sup>12</sup>**



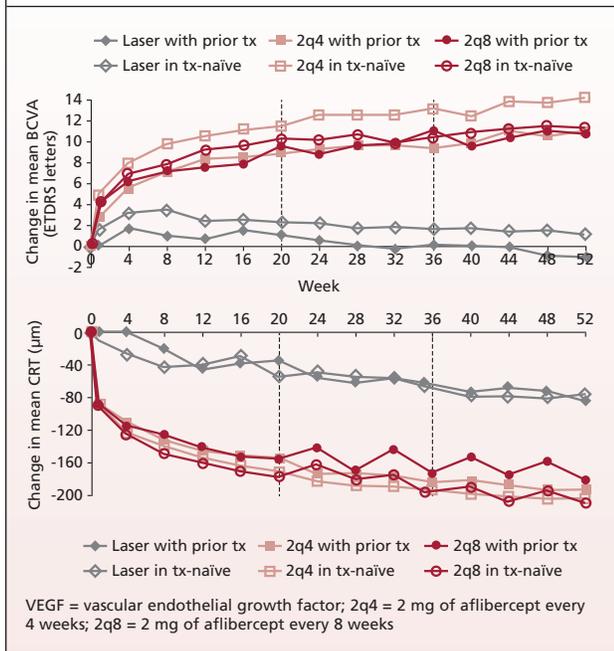
higher mean BCVA gain, while CRT alone cannot predict BCVA response. Thus, evaluation of morphological parameters on OCT and/or fluorescein angiography at baseline may be helpful in predicting functional and anatomical response to anti-VEGF therapy. Another subanalysis of the RESTORE study revealed that repeated intravitreal ranibizumab injections in patients with DME did not lead to progression of central microangiopathy or reduction in macular perfusion.<sup>16</sup> These results alleviate concerns that prolonged suppression of VEGF could be detrimental to microvascular integrity.

### Update on the VIVID-DME and VISTA-DME trials

The Phase III VIVID and VISTA trials (N=406 and 466, respectively) compare 2 intravitreal aflibercept regimens – 2 mg every 4 weeks (2q4) and 2 mg every 8 weeks (2q8) after 5 initial monthly doses – against laser photocoagulation in the treatment of DME. Fifty-two-week results presented at the 2013 EURETINA Congress<sup>17</sup> demonstrated the superiority of aflibercept over laser photocoagulation in BCVA endpoints. In his presentation of 2-year data from VIVID-DME and VISTA-DME,<sup>18</sup> Dr. David Brown showed that aflibercept was superior to laser with respect to mean changes in BCVA from baseline: +11.5 letters in the 2q4 group (average 21.3 injections) and +11.1 letters in the 2q8 group (average 13.5 injections), compared with 0.9 letters in the laser group. Gains of  $\geq 15$  letters at week 100 were seen in 38.3%, 33.1%, and 13.9% in the 2q4, 2q8, and laser groups, respectively. No new safety concerns were identified.

Dr. Quan Dong Nguyen presented an examination of the impact of previous anti-VEGF therapy on improvements in BCVA and CRT at week 52 in the VISTA trial.<sup>19</sup> He pointed out that in

**Figures 3A,B: VISTA-DME trial:<sup>19</sup> change in BCVA and CRT according to previous use of anti-VEGF therapy**



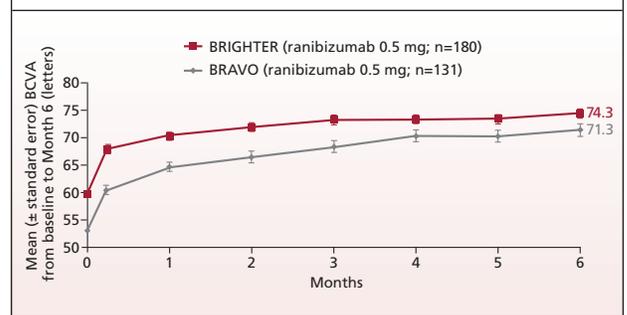
the VIVID trial, conducted outside the United States (US), only 10% of patients received prior anti-VEGF therapy, whereas approximately 43% of patients in the US-based VISTA trial were anti-VEGF experienced. The mean change in BCVA and CRT in the VISTA trial according to prior anti-VEGF use is shown in Figures 3A and 3B. The proportion of aflibercept-treated patients gaining  $\geq 15$  letters was highest in those receiving monthly aflibercept (48%) and lowest in anti-VEGF naïve patients treated with aflibercept every 8 weeks. About 32% of patients previously treated with anti-VEGF gained  $>15$  letters regardless of aflibercept dose.

Dr. Robert Avery presented differences in systemic pharmacokinetics following intravitreal administration of the 3 commonly used anti-VEGF agents in patients with DME.<sup>20</sup> Systemic exposure was highest following administration of bevacizumab, followed by aflibercept and lowest with ranibizumab, which is believed to be due to Fc recycling by Fc receptors on cells; as a Fab fragment, ranibizumab does not contain the Fc region. Consequently, free systemic VEGF measured at the third of 3 monthly doses was substantially lower with bevacizumab and aflibercept use than with ranibizumab. The impact of systemic exposure of intravitreal anti-VEGFs on the safety profile of these agents and the association with systemic adverse events is a source of ongoing debate within the medical community.<sup>21</sup>

### Support for Anti-VEGFs in the Management of Retinal Vein Occlusion (RVO)

Effectiveness of anti-VEGFs in RVO patients was recently confirmed in several small-scale clinical trials and observational studies with bevacizumab,<sup>22-24</sup> and in large, randomized clinical trials with ranibizumab<sup>25-28</sup> and aflibercept.<sup>29-31</sup> In BRAVO and CRUISE, VA gains achieved at 6 months with monthly ranibizumab injections were maintained with prn treatment at 12 months.<sup>27,28</sup> Subsequent trials with ranibizumab in RVO are being conducted to further address questions from these 2 pivotal trials. The open-label Phase IIIb BRIGHTER trial<sup>32</sup> is designed to evaluate the impact of concomitant laser on visual outcome and treatment frequency in patients on a prn ranibizumab regimen. There was a statistically significant difference in mean change in BCVA at 6 months from baseline with ranibizumab monotherapy (n=183; +14.8 letters) and

**Figure 4: Mean BCVA over 6 months and treatment exposure at Month 6 in patients treated with ranibizumab 0.5 mg in BRIGHTER and BRAVO<sup>32</sup>**



ranibizumab plus adjunctive laser (n=180; +14.1 letters) compared to laser treatment alone (n=92; 6.0 letters;  $P<0.0001$ ). At 6 months in BRAVO,<sup>23</sup> the improvements in BCVA with ranibizumab 0.3 mg and 0.5 mg were +16.6 letters and +18.3 letters, respectively. Figure 4 shows mean change in BCVA achieved with 0.5 mg ranibizumab in the BRIGHTER and BRAVO trials. Investigators also found similar response to ranibizumab in ischemic and nonischemic eyes.<sup>33</sup>

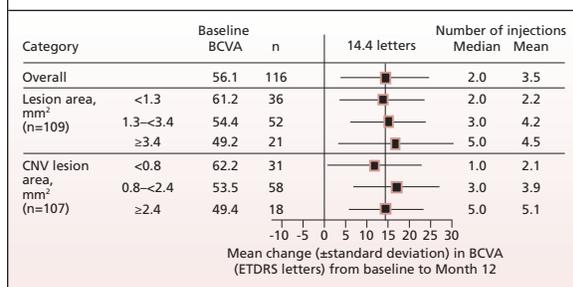
The VIBRANT trial,<sup>34</sup> a double-masked, active-controlled, randomized, Phase III trial, demonstrated superiority of aflibercept versus laser in 183 patients with BRVO. After 24 weeks of treatment, significantly more patients treated with aflibercept 2 mg every 4 weeks gained  $\geq 15$  letters from baseline compared to those treated with laser (53% versus 27%;  $P<0.001$ ). The mean improvements in BCVA from baseline to week 24 were 17.0 and 6.9 letters in the aflibercept and laser group, respectively ( $P<0.0001$ ), and the mean reduction in CRT from baseline to week 24 was 280.5  $\mu\text{m}$  with aflibercept versus 128.8  $\mu\text{m}$  with laser ( $P<0.0001$ ).

### Anti-VEGFs and Changes in the Myopic CNV (mCNV) Treatment Paradigms

mCNV is a common vision-threatening complication in young and middle-age adults worldwide.<sup>35</sup> Records from a longitudinal population-based database of more than 320 000 Canadian patients, analyzed between January 1, 2006, and December 31, 2011, estimated the prevalence of mCNV at 0.084% and the annual incidence at 0.0061%.<sup>36</sup> The most common treatments during this time period were laser photocoagulation (45%) and verteporfin (41%). Another epidemiology study that included 98 patients with mCNV recruited from 16 centres across Canada revealed that 32% had severe vision loss (VA  $\leq 20/200$ ) at the time of diagnosis, and another 19% had moderate vision loss (VA 20/80 to  $>20/200$ ).<sup>37</sup> In this study, almost all participants (91.8%) were treated with anti-VEGF therapy, receiving an average of 3.8 injections per year. In regard to CNV type, both studies report the highest occurrence of subfoveal CNV ( $>50\%$ ) and the least common was extrafoveal CNV (2%–6%).<sup>36,37</sup>

Anti-VEGF therapy continues to show promising results in the treatment of mCNV. Based on the results of the RADIANCE trial<sup>38</sup> in January 2014, Health Canada granted approval to ranibizumab for the treatment of visual impairment due to CNV secondary to pathologic myopia.<sup>39</sup> RADIANCE is a Phase III trial that assessed efficacy and safety of 2 different ranibizumab 0.5 mg dosing regimens in 277 patients with visual impairment (baseline VA 78.2 letters) due to mCNV: retreatment criteria were based on visual outcomes (Group 1) or disease activity (Group 2) versus verteporfin photodynamic therapy (vPDT; Group 3). Irrespective of retreatment criteria, ranibizumab provided superior BCVA gains versus vPDT over 12 months. A subgroup analysis of the trial<sup>40</sup> indicated an inter-patient variability with regard to treatment requirement, reinforcing the need for an individualized treatment approach. Patients with

**Figure 5: Treatment exposure and mean change in BCVA from baseline to Month 12 by baseline lesion area and CNV lesion area<sup>40</sup>**



larger lesions at baseline required more injections over the 12-month period to achieve similar BCVA improvements as the overall study population (Figure 5). Another *post hoc* exploratory subgroup analysis revealed that Asian mCNV patients tend to respond better to treatment with ranibizumab than Caucasian patients, including a numerically higher BCVA gain (16.1 versus 14.1), with 1 fewer injection (average 2.9 versus 3.8) over 12 months.<sup>41</sup> This is of particular importance due to the higher prevalence of mCNV in Asian patients: 10% with pathologic myopia develop CNV versus 5% of Caucasians.<sup>42,43</sup>

Results of the 48-week Phase III MYRROR trial<sup>44</sup> confirmed the superior efficacy of aflibercept 2 mg (n=91) over vPDT (n=31) in mCNV patients. Mean change in BCVA at 48 weeks was +13.5 letters with aflibercept versus +3.9 with vPDT. Notably, a median number of 2 anti-VEGF injections led to an average VA gain of 14 letters at 12 months in both the RADIANCE (mean 3.5 injections) and MYRROR trials (mean 4.0 injections).

### Applying Learning from Clinical Trials into Real-World Clinical Practice

LUMINOUS is a 5-year observational study across all approved ranibizumab indications.<sup>45</sup> It is the largest trial in retinal disease to date, and is being conducted in 41 countries, including Canada, with a target enrollment of 30 000 patients (treatment naïve or previously exposed to anti-VEGF treatment). LUMINOUS is designed to evaluate the long-term safety, efficacy, treatment patterns, and health-related quality of life outcomes in a real-life setting. Dr. Christopher Brand presented the baseline characteristics of the first 10 071 participants (825 from Canada),<sup>46</sup> and Dr. Paul Mitchell discussed results from the 1-year interim analysis.<sup>47</sup> The vast majority (93.1%) of study participants to date have wet AMD, followed by DME (4.5%), and RVO (1.2%). Of patients with wet AMD, 81.3% were previously treated with ranibizumab, and 17.7% were treatment-naïve. The mean patient age was 79.2 years and 61.7% were women. The cardiovascular risk profile of the LUMINOUS study population is representative of clinical practice; in wet AMD patients, 9% and 6% had previous heart attack and stroke, respectively, and 7% of DME patients had a history of heart attack or stroke. At baseline,

treatment-experienced patients had higher VA and lower CRT scores than treatment-naïve individuals. According to 1-year results in the first 2112 patients (including 47 Canadian participants), treatment-naïve patients gained 4.1 letters and treatment-experienced patients maintained their initial higher baseline VA (-1.1 letter score change). Both treatment-naïve and previously treated patients received a mean of 5.2 injections over 7.4 and 7.5 visits, respectively. No new safety signals were observed.

Using real-world 4-year utilization data with ranibizumab in the treatment of wet AMD in Canada (Figure 6), Gonder et al<sup>48</sup> suggest that many clinicians in Ontario and Quebec do not treat monthly but rather adopt an individualized ranibizumab treatment regimen to manage their AMD patients.

A retrospective cohort study was performed using US claims data that included patients who received first- or second-line intravitreal-anti-VEGF treatment with ranibizumab (n=912) or aflibercept (n=289) from November 18, 2011, to July 31, 2013.<sup>49</sup> This analysis indicated a similar number of injections at 12 months for first-line (5.04 aflibercept vs 5.02 ranibizumab) and second-line (5.72 aflibercept vs 5.76 ranibizumab) administration. Mean anti-VEGF costs related to first-line therapy were also comparable: \$10,288 for aflibercept vs \$9894 for ranibizumab. The rate of endophthalmitis was significantly higher among patients receiving aflibercept compared with ranibizumab (0.17% versus 0.08%; adjusted odds ratio 2.70).

## Conclusion

This recently presented evidence clearly illustrates the need for an individualized treatment approach in the management of retinal disease with few differences in the dosing frequency of currently available anti-VEGF therapies. It is clear that earlier treatment initiation carries significant VA benefits,

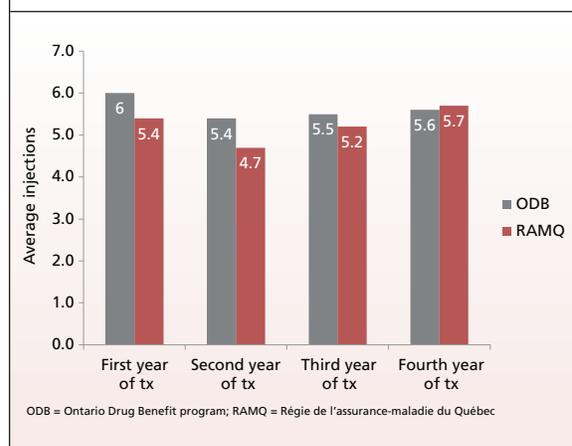
especially in patients with active disease indicated by the presence of fluid, cysts, and larger lesions. The predictive value of these morphological findings in regard to treatment regimen remains to be determined. At present, the treat-and-extend regimen appears to be a feasible and favourable approach used by many experts in this field.

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**Figure 6: Average number of injections for ranibizumab-naïve patients by Ontario and Quebec provincial drug plan<sup>48</sup>**



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