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Review Article

Treatment of diabetic retinopathy with anti-VEGF drugs

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ABSTRACT.

The aim of this review is to summarize the latest developments in the treatment of diabetic retinopathy (DR) with anti-vascular endothelial growth factor (VEGF) drugs. We reviewed recent studies that evaluated the role of the anti-VEGF agents bevacizumab, ranibizumab and pegaptanib in the treatment of DR. There was only one large randomized controlled trial that evaluated the role of ranibizumab in diabetic macular oedema (DME). Other prospective and retrospective studies provided important insight into the role of anti-VEGF drugs in DR, but most of them were not conducted in large scales. The growing evidence indicates that anti-VEGF drugs are beneficial in DR, especially in DME. Further studies are needed to fully evaluate the role of these agents, especially in proliferative DR and in DR candidates for vitrectomy surgery.

Key words: anti-VEGF – bevacizumab – diabetic retinopathy – macular oedema – ranibizumab

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Introduction

Diabetic retinopathy (DR) is the leading cause of blindness among working-age adults in the United States and one of the leading causes of blindness and visual impairment worldwide (Fong et al. 2004). Until recently, the armamentarium for treating DR included laser treatment, steroid injections and surgery. In the 1980s and 1990s, the results of the Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that focal/grid photocoagulation for clinically significant macular oedema (CSME) reduces the risk for moderate visual loss by 50% after 3 years of follow-up (Early Treatment Diabetic Retinopathy Study Research group 1985, 1991). The results of the Diabetic Retinopathy Study (DRS) demonstrated a 50% or greater reduction in the rate of severe visual loss in eyes treated with panretinal photocoagulation (PRP) for high-risk characteristic (HRC) proliferative diabetic retinopathy (PDR) after 5 years of follow-up (The Diabetic Retinopathy Study Research Group 1981). These studies continue to be the mainstays of the treatment of DR until today. In more severe cases, such as nonclearing vitreous haemorrhage (VH) or tractional retinal detachment (TRD), pars plana vitrectomy (PPV) may result in improvement in visual acuity (VA) (Diabetic Retinopathy Vitrectomy Study Research group 1990) as may intravitreal steroid injections for persistent diabetic macular oedema (DME).

The revolutionary results of the treatment of neovascular age-related macular degeneration (AMD) with ranibizumab that were published in 2006 (Brown et al. 2006; Rosenfeld et al. 2006) encouraged researchers to investigate the role of anti-vascular endothelial growth factor (VEGF) drugs in DR as well. Three major anti-VEGF drugs were suggested for the treatment of DR. In December, 2004, pegaptanib (Macugen) became the first anti-VEGF drug approved by the US Food and Drug Administration (FDA) for intravitreal injection in the treatment of neovascular AMD. This drug, which is an aptamer, is targeted against only one isoform of VEGF (VEGF-165), and some earlier studies suggested that it may also be beneficial for DME (Cunningham et al. 2005; Querques et al. 2009). Its current use, however, is rather limited because of the availability of other anti-VEGF agents that are targeted against all active forms of VEGF-A. Ranibizumab (Lucentis), a recombinant humanized monoclonal antibody fragment, was specifically designed for ophthalmic use. This drug was approved by the FDA for the treatment of neovascular AMD, but it is relatively costly. Bevacizumab (Avastin), a full-length anti-VEGF antibody, was originally formulated for intravenous administration in the treatment of colon cancer.

The low-cost off-label use of intravitreal injections of bevacizumab encouraged many physicians to use this drug mainly for AMD as well as for other retinal pathologies (Waisbourd et al. 2007). The aim of this review is to provide updated data on the treatment of DR with anti-VEGF agents.

Anti-VEGF Agents for DME

The recently published results of the DR Clinical Research network (DRCR net) for evaluating the role of ranibizumab and triamcinolone (Kenalog) in DME (Protocol I) provided one of the important cornerstones in the treatment DR. This randomized, large-scale multicenter clinical trial, supported by the American National Eye Institute/National Institute of Health (NEI/NIH), evaluated the efficacy and safety of 0.5 mg intravitreal ranibizumab plus prompt (within 1 week) or deferred laser (≥24 week), or 4 mg intravitreal triamcinolone plus prompt (within 1 week) laser and compared the results with sham plus prompt laser treatment (Table 1). A total of 854 eyes (691 participants) were enrolled in the study, and 87% of them completed the 2-year follow-up. The underlying rationale of the treatment algorithm was to continue treatment as needed until stabilization, or no further improvement was noted. The difference in mean change in VA from the sham plus prompt laser treatment at 2 years was +5 letters for the ranibizumab plus prompt laser group ($p = 0.01$), +7.2 letters for the ranibizumab plus deferred laser group ($p < 0.001$) and −1.6 for the triamcinolone plus prompt laser group ($p = 0.43$). The difference in mean retinal thickening change from sham plus laser group at 2 years was −31 μm for the ranibizumab plus prompt laser group ($p = 0.01$), −36 μm for the ranibizumab plus deferred laser group ($p = 0.004$) and −3 μm for the triamcinolone plus prompt laser group ($p = 0.81$). The results of this study suggested that ranibizumab should be considered for patients with DME and the characteristics similar to those of the subjects in that clinical trial (The Diabetic Retinopathy Clinical Research Network 2010; Elman et al. 2010). This important study (DRCR net protocol I) differed from the previously conducted DRCR net protocol B study, a randomized trial that compared intravitreal triamcinolone and laser photocoagulation for DME. The Protocol B study showed superiority of the focal/grid photocoagulation when compared with intravitreal triamcinolone for most patients with DME who had characteristics similar to the cohort in this trial (The Diabetic Retinopathy Clinical Research Network 2008).

Nguyen et al. randomized 126 patients with DME to receive ranibizumab (baseline, months 1, 3 and 5), laser (baseline and month 3 if needed) or a combination (baseline, month 3). In this phase 2 study, the mean gain in VA at month 6 was significantly greater in the ranibizumab group (+7.24 letters, $p = 0.01$,) compared with the laser group (−0.43 letters), while the gain in the combination group (+3.80 letters) was not significantly different from that of other groups. Excess foveal thickness was reduced by 50%, 33% and 45%, respectively, suggesting that ranibizumab alone, according to their protocol, is a better option than laser in this short-term trial (READ-2 study) (Nguyen et al. 2009). The RESOLVE trial, a 12-month randomized control trial, involved 151 DME patients treated over 12 months with 6 mg/ml ranibizumab ($n = 51$), 10 mg/ml ranibizumab ($n = 51$) or sham injection ($n = 49$). Three initial monthly injections were followed by retreatment based on success, futility or safety criteria. The mean average best corrected visual acuity (BCVA) change from baseline was +7.8 letters for ranibizumab (pooled groups) versus −0.1 letters for the sham group ($p < 0.0001$). (Hansen & Resolve Study Group 2010)

Other studies, conducted for shorter periods of time, also supported the use of ranibizumab for DME (Chun et al. 2006). Additional phase 3 studies are currently ongoing; the initial results of the RESTORE trial (ClinicalTrials.gov: NCT00687804) that is evaluating the efficacy and safety of ranibizumab in patients with visual impairment owing to DME were recently released. That study found that 37% of patients treated with ranibizumab alone and 43% of those treated with ranibizumab plus laser therapy gained a substantial vision improvement of 10 letters or more compared with 16% of patients treated with laser alone after 1 year (http://clinicaltrials.pharmaceutical-business-review.com/news/novartis_releases_ranibizumab_restore_phase_iii_study_results_100524/). The RISE trial (NCT00473330) and the RIDE trial (NCT00473382) evaluated the use of ranibizumab in subjects with CSME with centre involvement. The estimated date for primary completion of their data is expected in 2012.

The use of bevacizumab has also been investigated in DME. Michaelides et al. 2010 prospectively evaluated 80 eyes of 80 patients with

Table 1. Summary of the 2- year results of the Diabetic Retinopathy Clinical Research Network Randomized Trial for evaluating ranibizumab plus prompt (within 1 week) or deferred laser (≥24 weeks) or triamcinolone plus prompt laser for DME.

Inclusion criteria (854 eyes randomized)	At least one eye meeting all of the following criteria: ETDRS BCVA approximately 20/32 to 20/320 Definite retinal thickening owing to DME involving the centre of the macula on clinical examination Central subfield ≥250 μm		
Difference in mean VA change from Sham + Prompt Laser	Ranibizumab + Prompt Laser +5.0 letters [$p = 0.01$]	Ranibizumab + Deferred Laser +7.2 letters [$p < 0.001$]	Triamcinolone + Prompt Laser −1.6 letters [$p = 0.43$]
Difference in mean OCT thickening change from Sham + Prompt Laser	Ranibizumab + Prompt Laser −31 μm [$p = 0.01$]	Ranibizumab + Deferred Laser −36 μm [$p = 0.004$]	Triamcinolone + Prompt Laser −3 μm [$p = 0.81$]
Rationale of the treatment algorithm	To continue treatment, as needed, until stabilization or lack of further improvement is noted.		

ETDRS = early treatment diabetic retinopathy study, VA = visual acuity, BCVA = best corrected visual acuity, OCT = optical coherence tomography, DME = diabetic macular oedema.

centre involving CSME for 1 year (BOLT study). In that masked study, patients were randomized to either bevacizumab (6 weekly; minimum of three injections and maximum of nine injections in the first 12 months) or macular laser therapy (4 monthly; minimum of one treatment and maximum of four treatments in the first 12 months). At 12 months, the bevacizumab group had gained a median of 8 ETDRS letters, whereas the laser group lost a median of 0.5 ETDRS letters ($p = 0.0002$). The mean central macular thickness (CMT) decreased from 507 μm at baseline to 378 μm ($p < 0.001$) in the bevacizumab group, whereas it decreased from 481 to 413 μm in the laser group ($p = 0.02$) (Michaelides et al. 2010).

Kook et al. (2008) found that a long-term decrease in CMT and a gain in VA can be observed following repeated intravitreal injections of bevacizumab even in cases with chronic diffuse ischaemic DME. Other studies found no difference between intravitreal bevacizumab at doses of 1.25 or 2.5 mg (Arevalo et al. 2009a,b Lam et al. 2009). The combination therapy of bevacizumab with triamcinolone was also evaluated by several groups. Soheilian et al. randomized 150 eyes of 129 patients with CSME to three arms: bevacizumab 1.25 mg alone, a combination of bevacizumab with triamcinolone 2 mg and a laser group. Retreatment was performed at 12-week intervals whenever indicated. At 24 weeks, the bevacizumab group yielded better visual outcomes when compared to the laser treatment, but no adjunctive effect of triamcinolone was demonstrated (Soheilian et al. 2009). Shimura et al. (2008), however, found better results in reducing DME and in the improvement in VA with triamcinolone when compared with bevacizumab. Paccola et al. (2008) also suggested that one single injection of triamcinolone may offer certain advantages over bevacizumab in the short-term management of refractory DME, and others suggested only short-term effect to the conjunction of triamcinolone to bevacizumab (Ahmadieh et al. 2008; Faghihi et al. 2008). Intravitreal administration of triamcinolone may, however, result in intraocular pressure (IOP) elevation as well as formation or progression of cataract.

The recent results of the DRCR net study cited earlier suggested that treatment of intravitreal triamcinolone combined with laser did not result in superior VA outcomes compared with laser alone. In an analysis limited to pseudophakic eyes, the triamcinolone group's outcome for VA appeared to be similar to that of the ranibizumab groups, but it was associated with an increased risk of IOP elevation.

Pegaptanib was also evaluated in patients with DME in a phase 3 multicentre randomized controlled trial (NCT00605280). Two hundred and sixty patients with DME received pegaptanib or sham procedure every 6 weeks in year 1. In year 2, subjects could receive injections according to prespecified criteria. Up to three focal or grid laser treatments per year were permitted beginning at week 18. Positive results were recently published, showing 10 letter gains in 37% of patients who received pegaptanib compared with 20% of patients receiving sham treatment at 54 weeks ($p = 0.0047$). At the end of year 2, mean VA improved in 6.1 letters in the pegaptanib group compared with 1.3 letters in the sham group ($p < 0.01$). (http://www.eyetech.com/content/pr/Eyetech_News_Release%20_WOC_FINAL_06_05%2010.pdf).

Safety issues

Sight-threatening adverse events of intravitreal injections of anti-VEGF drugs are very rare and include endophthalmitis and retinal detachment (Waisbourd et al. 2007). In the DRCR net study, the endophthalmitis cases related to the drug injection in the ranibizumab groups were 0.08% of all injections given. There was also a single case of traction retinal detachment in a patient with PDR and prior PRP treatment at baseline (< 1%). In their case report, Chen et al. (2009) suggested that intravitreal bevacizumab may also result in acute reduction in VA in chronic DME by disrupting an already fragile vascular perfusion status, leading to macular ischaemia, as demonstrated by enlargement of the foveal avascular zone and persistent late leakage on fluorescein angiogram. Altogether, there is cumulating evidence that anti-VEGF drugs may be beneficial in the treatment of DME, especially after the publication of the 2-year results of the DRCR net study.

Anti-VEGF Agents for PDR

Anti-VEGF agents have also been studied for the treatment of PDR. Unlike DME, the data available for these agents in PDR are relatively limited, and no large prospective randomized studies have been published thus far. Avery et al. retrospectively evaluated 44 PDR eyes that had been treated with intravitreal bevacizumab. All of their studied eyes had complete or partial reduction in fluorescein angiography (FA) leakage of the neovascularization within 1 week after the injection. Complete resolution of neovascularization of the disc (NVD) was noted in 73% of the treated eyes (Avery et al. 2006). Mirshahi et al. (2008) prospectively evaluated 80 eyes of 40 HRC PDR patients in a fellow-eye sham controlled trial. Bevacizumab 1.25 mg was administered at their first session of laser treatment. A total of 87.5% of the bevacizumab-injected eyes and 25% of the sham group eyes showed complete neovascularization regression at week 6 ($p < 0.005$). At week 16, however, the protective effect of bevacizumab was diminished, and the regression rate in the two groups became identical (25%; $p = 1.000$). Cho et al. prospectively evaluated 40 eyes with PDR and found that the eyes that received PRP treatment alone had significantly worse VA at 3 months ($p = 0.041$), whereas the eyes that received PRP plus bevacizumab underwent no significant change in VA. The proportion of eyes that developed VH was also significantly lower in the PRP plus bevacizumab group ($p = 0.023$) (Cho et al. 2009). Schmidinger suggested that a three monthly bevacizumab retreatment regime might be a valid method to control persistent neovascularization (NV) in PDR patients (Schmidinger et al. 2009), and Arevalo et al. found no safety concerns for both 1.25 and 2.5 mg doses (Arevalo et al. 2009c). Other groups found bevacizumab to be beneficial in PDR patients as well (Jorge et al. 2006; Tonello et al. 2008; Erdol et al. 2010), although some suggested that this procedure may increase the risk of TRD in eyes with fibrous proliferation (Moradian et al. 2008).

The use of anti-VEGF agents prior to or in tandem with PRP may prevent

DME occurrence secondary to the PRP: Cho et al. (2009) found that in PDR patients undergoing PRP, adjunction of bevacizumab before laser treatment resulted in a significant reduction in CMT at 1 and 3 months compared with PRP alone. In PDR patients with complete PRP undergoing bevacizumab injections for persistent new vessels, a decrease in mean CMT was found after 6 months when compared to baseline (Schmidinger et al. 2009).

Bevacizumab was also shown to be effective in PDR patients with VH. Huang et al. administered bevacizumab to 40 patients with VH, followed by PRP when technically possible. A second injection was given after 4–6 weeks if that VH was not decreased. PPV was performed if the VH persisted >12 weeks. Vitreous clear-up time was 11.9 weeks in the study group and 18.1 weeks in a historical control group ($p = 0.02$). The rates of required vitrectomy were 10% in the study group and 45% in the control group ($p = 0.01$) (Huang et al. 2009).

Pegaptanib was also studied for PDR patients in a retrospective analysis of individuals with retinal NV identified from a large trial evaluating pegaptanib for the treatment of DME. Most of the patients with retinal NV who received this drug showed regression by week 36 (Adamis et al. 2006).

It would appear that the role of anti-VEGF drugs is important in PDR, but it remains uncertain what should be the exact treatment protocol for these agents. Large prospective studies are needed to determine the exact role of these drugs. Currently, the gold standard for the treatment of PDR remains PRP, while anti-VEGF agents can play a role as an adjunctive therapy in severe or persistent cases.

Anti-VEGF Agents in Adjunction to PPV

Recent studies demonstrated a few benefits of using anti-VEGF drugs preoperatively for PDR. In most studies, bevacizumab was administered for no longer than 1 week preoperatively, because TRD may occur or progress shortly following the administration of bevacizumab in patients with severe PDR (Arevalo et al. 2008; Moradian et al. 2008). Ahmadieh et al. prospectively evaluated 68 eyes undergoing PPV for the management of PDR complications. Their study patients were randomly assigned to bevacizumab 1.25 mg or sham injections 1 week preoperatively. The incidence of postvitrectomy haemorrhage at 1 week and at 1 month after surgery was significantly lower in the bevacizumab group compared with the control group ($p = 0.023$ and $p = 0.001$, respectively) (Ahmadieh et al. 2009). di Lauro et al. (2010) also found that the administration of bevacizumab 1 week preoperatively reduced retinal and iritic NV, thus making surgery easier and safer and improving the anatomical and functional prognosis. Others have also suggested that preoperative bevacizumab facilitates surgery and improves surgical outcomes (Yeh et al. 2009; Rizzo et al. 2008; da et al. 2009; Modarres et al. 2009; Romano et al. 2009a), although intraoperative bevacizumab was not found helpful in preventing the recurrence of VH (Romano et al. 2009b). Oshima et al. (2009) suggested that microincision vitrectomy surgery plus bevacizumab offers comparable anatomical success compared with conventional 20-gauge PPV in patients with TRD, with shorter surgical time, fewer intraoperative complications and favourable visual recovery. The results of these studies appear to indicate that the administration of bevacizumab, a few days preoperatively, may provide substantial advantage among patients with PDR.

Conclusions

Similar to the revolution in the treatment of AMD with ranibizumab following the MARINA and ANCHOR studies (Brown et al. 2006; Rosenfeld et al. 2006), the recently published results of the DRCR net show promise to revolutionize the treatment of DME patients. There is also growing evidence that anti-VEGF drugs are beneficial among patients with active PDR, including those who are candidates for surgery, although large randomized controlled trials need to be performed to determine when treatment should be initiated, what should be the recommended treatment intervals and when treatment should be withheld.

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