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Diabetic macular edema: Efficacy and safety of anti-vascular endothelial growth factor therapy

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Abstract

Diabetic retinopathy is one of the prominent causes of vision impairment in the working-age population in industrialized countries and is related to 1%-5% of cases of blindness in the world. Among patients with diabetic retinopathy, diabetic macular edema (DME) is the major reason of vision impairment and represents a significant public health problem. Previous studies demonstrated the role of vascular endothelial growth factor (VEGF) in diabetic retinopathy and DME pathogenesis, and also revealed the efficacy of anti-VEGF agents for the management of these disorders. This review summarizes the outcomes of clinical studies that evaluated the anti-VEGF therapy including pegaptanib, ranibizumab, bevacizumab, and aflibercept for the management of DME. A significant number of clinical trials indicated favorable functional and anatomical results of anti-VEGF therapy for DME. Therefore, these agents should be considered an option in the treatment of DME in routine clinical practice.

Key words: Anti-vascular endothelial growth factor; Aflibercept; Bevacizumab; Diabetic macular edema; Pegabtanib; Ranibizumab

Core tip: Diabetic retinopathy is one of the prominent reasons of vision loss in the industrial countries. Among these patients, diabetic macular edema (DME) is the main reason of vision impairment. Previous studies have shown that vascular endothelial growth factor (VEGF) has a major role in the pathogenesis of diabetic retinopathy and DME, as well as demonstrated favorable results for DME treatment. This review summarizes the outcomes of clinical trials that evaluated anti-VEGF agents including pegaptanib, ranibizumab, bevacizumab, and aflibercept in DME treatment.

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INTRODUCTION

Diabetic retinopathy is the main reason of visual impairment in the industrial countries and is related to 1%-5% of cases of blindness worldwide[1]. The main reason of vision decrement in diabetic retinopathy is diabetic macular edema (DME) which could be detected during non-proliferative or proliferative stage[2,3]. According to the Wisconsin Epidemiologic Study of Diabetic Retinopathy, the prevalence of DME was 20.1% for type Ⅰ diabetes mellitus and 25.4% for type 2 diabetes mellitus receiving insulin treatment[4].

DME is generally classified into two subtypes. First is the focal edema which consists of localized areas of retinal thickening originating from the leaking micro-aneurysms and is generally associated with hard exudates. Second is the diffuse macular edema which consists of generalized leakage of dilated capillaries and disrupted retinal pigment epithelial barrier[5,6].

DME is associated with hypertension, poor blood glucose regulation, cardiovascular disease, impaired renal function, increased number of microaneurysms and vitreomacular traction[7,8]. Regulation of blood glucose level, systemic hypertension and hyperlipidemia along with following the at-risk patients are the most efficient ways to prevent the vision loss from diabetic retinopathy[2,9].

The gold standard treatment for DME has been macular photocoagulation (MPC) in recent decades[10]. The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that approximately 40% of the patients had achieved ⩾ 6 letters in best corrected visual acuity (BCVA) with focal laser treatment in 3 years[10,11]. Recently, the Diabetic Retinopathy Clinical Research Network (DRCR.net) has demonstrated BCVA improvement of more than 5 letters of vision in 51%, 47% and 62% of eyes treated with MPC after 1, 2 and 3 years of follow-up, respectively[12].

In recent years, alternative or adjunct treatments for DME have been studied, and various pharmacological compounds are under investigation, such as therapies using inhibitors of VEGF[13,14]. The purpose of this assessment is to review the evidence for current anti-VEGF pharmacotherapies in the treatment of DME.

ANTI-VEGF AGENTS FOR DME

The expression of VEGF which stimulates angiogenesis, inflammation and vascular permeability increases due to hypoxia[15]. VEGF molecule breaks down the blood-retinal barrier by its distracting impact on the endothelial zona occludens and induction of fenestrations on the endothelial cells[16,17]. In addition, VEGF causes degeneration in endothelial basement membranes which deteriorate the structure of the retinal microvessels with leakage of blood plasma proteins into the extracellular space[18,19]. The proinflammatory effect of VEGF is related to over-expression of intercellular adhesion molecule-1 which leads leucocyte adhesion to the vascular endothelium, capillary occlusion and endothelial cell apoptosis[20]. VEGF 165 is the leading isoform which is most associated with the increased angiogenesis and vascular permeability[21]. Therefore, VEGF inhibition may be an effective option for management of DME. Several studies have been conducted that have addressed the efficacy and safety of anti-VEGF agents, including ranibizumab (Lucentis, Genentech, Inc., United States), pegaptanib (Macugen, OSI/Eyetech, United States), aflibercept (EYLEA; Regeneron, United States) and bevacizumab (Avastin, Genentech, Inc., United States), in the treatment of DME (Table 1).

CLINICAL TRIALS FOR DME

Pegaptanib sodium (macugen)

Pegaptanib is the first intravitreal VEGF antagonist drug that was approved by the Food and Drug Administration (FDA) for the management of exudative age related macular degeneration (AMD). This molecule is 28-nucleotide chemically synthesized single-stranded nucleic acid (aptamer) that only targets the VEGF 165 isoform[22].

Macugen Diabetic Retinopathy Study Group (a double-masked multicenter controlled phase 2 randomized clinical trial) evaluated the efficacy of pegaptanib in DME[23]. Totally 172 patients with DME who were randomly divided into four arms were enrolled: 0.3, 1, 3 mg intravitreal pegaptanib or sham. Intravitreal pegabtanib injections were administered at weeks 0, 6 and 12. After week 12, additional injections could be performed according to the discrimination of the investigators. In addition focal laser treatment could be chosen as a beginning at week 13. At week 36, better results were achieved in BCVA, central foveal thickness (CFT) and need for additional MPC, in the pegaptanib groups compared to the sham group, in particular the 0.3 mg group. In addition, the better improvements in the pegabtanib groups were determined despite the fact that focal or grid laser was applied 23% more to the sham group between weeks 12 and 36. The proportion of improvements in BCVA was 73% in the 0.3 mg pegabtanib group whereas 51% in the sham group. In detail, the mean increase in BCVA was 4.7 letters and 18% gained 3 or more Snellen lines for the 0.3 mg pegabtanib group. A phase 2/3 randomized, controlled, multicenter trial compared the affectivity and safety of 0.3 mg pegaptanib (administrated for every 6 wk for two years) and sham injections in patients with DME[24]. The total number of subjects included in the first and second year analyses were 260 (133 pegaptanib, 127 sham) and 207 (107 pegaptanib, 100 sham), respectively. The number of patients who gained ⩾ 10 letters in BCVA were 49 (36.8%) and 25 (19.7%) for the pegaptanib and sham groups, respectively, at week 54. At year 1, the BCVA was significantly ($P < 0.05$) improved in the pegaptanib group (gained 5.2 letters) compared to sham (gained 1.2 letters). At year 2, these were 6.1 letters in the pegaptanib group and 1.3 letters in the sham arm ($P < 0.01$).

Table 1 Major trials of anti-vascular endothelial growth factor drugs for diabetic macular edema

Ref.	Drug	Design	*n*	Treatment regimen	Follow-up	Results
Sultan *et al*[24]	Pegaptanib	Phase 2/3, randomized, sham-controlled, multicenter	260 patients	(1) 0.3 mg IVP; or (2) sham injections at baseline and every 6 wk in year 1 and focal/grid laser beginning at wk 18. In year 2, (1) 0.3 mg IVP; or (2) sham up to every 6 wk PRN	2 yr	Improvement of ≥ 10 letters at 54 wk: (1) 36.8%; and (2) 19.7% (P = 0.0047). BCVA letters gained at week 102: (1) 6.1 letters; and (2) 1.3 letters (P < 0.01). No significant difference in CFT decreases at 54 and 102 wk between (1) and (2)
Macugen Diabetic Retinopathy Study Group[23]	Pegaptanib	Phase 2, randomized, double-masked, dose-ranging, controlled	172 patients	(1) 0.3 mg PEG; or (2) sham at baseline, week 6 and week 12; additional injections or focal LPC as needed for an additional 18 wk	36 wk	Mean VA at week 36: (1) 20/50; and (2) 20/63 (P = 0.04). Ten letters gained: (1) 34%; and (2) 10% (P = 0.003). CRT at week 36: (1) -68 μm; and (2) +4 μm (P = 0.02). PEG doses of 0.3, 1, 3 mg all well tolerated
Elman *et al*[28] (DRCR)	Ranibizumab	Randomized, prospective, multicenter	854 eyes of 691 patients	(1) 0.5 mg IVR plus prompt laser; (2) 0.5 mg IVR plus deferred laser (> 24 wk); and (3) 4 mg IVT plus prompt laser; (D) sham injection plus prompt laser	1 yr	Mean VA letter improvement at 1 yr: (1) +9 ± 1, P < 0.001; (2) +9 ± 12, P < 0.001; (3) +4 ± 13, P = 0.31; and (4) +3 ± 13
Mitchell *et al*[33] (RESTORE)	Ranibizumab	Randomized, prospective, multicenter	345 patients	(1) 0.5 mg IVR monthly × 3 then PRN + sham laser; (2) 0.5 mg IVR monthly × 3 then PRN + laser; and (3) sham injections + laser	12 mo	VA better for (1) and (2) from months 1 to 12 compared with (3); 12-mo VA: (1) +6.1 letters; (2) +5.9 letters; and (3) +0.8 letters (P < 0.0001 for both); BCVA 20/40 or better: (1) 53%; (2) 44.9%; and (3) 23.6%. No significant differences between (1) and (2) at 12 mo
RISE Trial[31]	Ranibizumab	Phase 3, randomized, sham-controlled, multicenter	377 patients	(1) 0.3 mg IVR; (2) 0.5 mg IVR; and (3) sham injection. All given monthly injections × 24 mo and with rescue laser available at 3 mo	2 yr	Improvement of ≥ 15 letters at 2 yr: (1) 44.8% (56/125); (2) 39.2% (49/125); and (3) 18.1% (23/127). Statistically significant for both (1) and (2) compared with (3) at P < 0.001 and P < 0.002, respectively
RIDE Trial[31]	Ranibizumab	Phase 3, randomized, sham-controlled, multicenter	382 patients	(1) 0.3 mg IVR; (2) 0.5 mg IVR; and (3) sham injection. All given monthly injections × 24 mo and with rescue laser available at 3 mo	2 yr	Improvement of ≥ 15 letters at 2 yr: (1) 33.6% (42/125); (2) 45.7% (58/127); and (3) 12.3% (16/130). Statistically significant for both (1) and (2) compared with (3) at P < 0.001
Massin *et al*[27] (RESOLVE)	Ranibizumab	Phase 2, randomized, sham controlled, multicenter	151 patients	(1) 0.3 mg or 0.5 mg IVR monthly × 3 mo then as needed (dose doubling allowed after 1 mo); or (2) sham injection monthly × 3 mo then as needed (as-needed rescue LPC in)	1 yr	Month 12 mean ± SD BCVA change: (1) 10.3 ± 9.1 letters; and (2) -1.4 ± 14.2 letters; P < 0.001. Gain ≥ 10 letters: (1) 60.8%; and (2) 18.4% (P < 0.001). Mean change in CFT: (1) -194.2 μm; and (2) -48.4 μm (P < 0.001)
DRCR[41]	Bevacizumab	Randomized, prospective	121 patients	(1) Focal LPC; (2) IVB 1.25 mg at baseline and 6 wk; (3) 2.5 mg IVB at baseline and 6 wk; (4) 1.25 IVB at baseline and sham at 6 wk; or (5) 1.25 IVB at baseline and 6 wk with focal LPC	24 wk	Baseline CFT: 411 μm; at 3 wk, CFT reduction greater in (2) and (3) than in (1); CFT reduced > 11% at 3 wk in 43% of IVB-treated eyes and 28% of LPC treated eyes, and at 6 wk in 37% of IVB treated eyes and 50% of LPC-treated eyes. Mean 12-wk VA improvement in (2) and (3) of 1 line better than (1). No significant short-term benefit combining IVB and laser
Michaelides *et al*[42], 2012 (BOLT)	Bevacizumab	Randomized, prospective	80 patients	(1) Focal/grid laser; or (2) IVB 1.25 mg at baseline, 6 and 12 wk, then as needed	24 mo	Mean gains in BCVA at 24 mo: (1) +2.5 letters; and (2) +9 letters (P = 0.005). Mean change in CFT at 24 mo; (1) -118 μm; and (2) -146 μm
Do DV *et al*[38], 2012 (DA VINCI)	Aflibercept	Phase 2, randomized, multicenter	221 patients	VEGF Trap-Eye (1) 0.5 mg every 4 wk (0.5q4); (2) 2 mg every 4 wk (2q4); (3) 2 mg every 8 wk after 3 initial monthly doses (2q8); (4) 2 mg dosing as needed after 3 initial monthly doses (2PRN); or (5) macular laser photocoagulation.	2 yr	Mean improvements in BCVA in the VEGF Trap-Eye groups at week 52 were 11.0, 13.1, 9.7, and 12.0 letters for 0.5q4, 2q4, 2q8, and 2PRN regimens, respectively, *vs* -1.3 letters for the laser group (P ≤ 0.001 *vs* laser)

BCVA: Best-corrected visual acuity; CFT: Central foveal thickness; DRCR: Diabetic Retinopathy Clinical Research Network; IVB: Intravitreal bevacizumab; PRN: Pro re nata; IVP: Intravitreal pegaptanib; IVR: Intravitreal ranibizumab; IVT: Intravitreal triamcinolone; LPC: Laser photocoagulation; VEGF: Vascular endothelial growth factor.

Ranibizumab (lucentis)

Ranibizumab is a humanized antibody fragment which shows affinity to all VEGF-A isoforms. In 2006, Nguyen *et al*[22] showed the crucial effect of VEGF in DME pathogenesis for the first time and suggested that application of VEGF antagonists such as ranibizumab may reduce retinal edema. Major clinical trials compared the affectivity and safety of ranibizumab with sham or with laser photocoagulation and intravitreal triamcinolone acetonide (IVTA).

The READ-2 study demonstrated that intravitreal ranibizumab achieved better visual results compared to

photocoagulation[25]. Subjects were randomly divided into three groups: 0.5 mg ranibizumab (group 1), focal or grid laser photocoagulation (group 2), or laser plus ranibizumab (group 3). The mean improvement in BCVA was 7.24, 0.43, and 3.8 letters after the primary end point at month 6. At month 24 these were 7.7, 5.1, and 6.8 letters, respectively. The CFT values at month 24 were 340 μm, 286 μm, and 258 μm, respectively. In the ranibizumab group, the mean BCVA (ΔBCVA letters = 3.1, P = 0.009) and CFT (ΔCFT = 70 μm, P = 0.006) were significantly improved at month 36 compared to month 24. However, these were not statistically significant in the laser (-1.6 letters and -36 μm, respectively) and the ranibizumab + laser groups (+2.0 letters and -24 μm). This study showed that long-term results of ranibizumab therapy for DME are favorable, however, injections should be performed frequently in many patients to control edema and maintain the vision[26].

The safety and efficacy of ranibizumab in diabetic macular edema with center involvement study was a multi-center, randomized trial including 151 patients who were administrated either sham, ranibizumab 0.3 mg, or ranibizumab 0.5 mg injections monthly for 3 mo and followed by PRN (Pro Re Nata) treatment[27]. Ranibizumab was increased to 0.6 mg and 1 mg, respectively, if the CFT persisted > 300 μm at the first month or if the CFT was > 225 μm with a decrease in CFT < 50 μm compared to the preceding measurement at any visit following the baseline injection. The injections were interrupted at any monthly visit following the third injection if the CFT was < 225 μm and the BCVA was > 79 letters. The injections were restarted if the CFT increased by > 50 μm or the BCVA worsened ⩾ 5 letters and was < 74 letters. At 12 mo, the improvement in BCVA was 10.2 letters in the ranibizumab group whereas decreased 1 letter in the sham group. Regarding the change in CFT, it was decreased 200 μm in the ranibizumab group and 40 μm in the sham group. The crucial point of this study is to evaluate the outcome of ranibizumab retreatment strategy that could be applicable in clinical practice.

The DRCR.net is a multicenter, randomized clinical trial evaluating whether ranibizumab combined with prompt (within 10 d) or deferred (no sooner than 6 mo) laser, and IVTA combined with prompt laser, might improve BCVA compared to focal/grid photocoagulation alone in central involved DME. At the first year, the mean BCVA significantly improved both in the ranibizumab + prompt laser (+9 ± 11 letters, P < 0.001) and the ranibizumab + deferred laser (+9 ± 12 letters, P < 0.001) groups, however, it was not in the triamcinolone + prompt laser group (+4 ± 13 letters, P = 0.31) compared to the sham + prompt laser group (+3 ± 13 letters). The mean decrease in the CFT was similar between the triamcinolone + prompt laser group and both ranibizumab groups. In addition, these were greater compared to the sham + prompt laser group. Regarding the 3-year results, ranibizumab + prompt laser therapy did not show better BCVA outcomes, and possibly worse, compared to the ranibizumab + deferred laser. They suggested that these BCVA differences may be associated with fewer cumulative ranibizumab injections in the prompt laser treatment group during the follow-up period[28,29]. The 5-year results have recently been reported[30]. The mean BCVA improvement was 7.2 letters in ranibizumab + prompt laser group and 9.8 letters in the ranibizumab + deferred laser group (mean difference was -2.6 letters, P = 0.09). No additional laser treatment was performed in 56% of patients from the deferred laser group during the 5-year follow-up period. The median number of injections in the prompt and deferral groups was 13 and 17, respectively. The percentage of patients receiving no injections in the prompt and deferral groups were 54% and 45% during 4 years of follow-up, respectively, and 62% and 52% during 5 years of follow-up, respectively. The 5-year results demonstrated that BCVA was not significantly different between the ranibizumab + prompt laser and ranibizumab + deferred laser treatment groups. Despite the fact that half of the eyes from the deferred laser treatment group did not receive additional laser treatment during 5 years, more injections were administrated in such eyes to achieve these results. Finally the BCVA improvement was sustained in most eyes from year 1 to 5 with a small number injection after the year 3 in both ranibizumab groups.

The RISE and RIDE are parallel, phase 3, multicenter, sham controlled, randomized studies comparing sham injections with 0.3 or 0.5 mg ranibizumab injections on a monthly basis for 24 mo[31]. Macular laser was available per-protocol–specified criteria. The RISE study showed that the percentage of patients gaining ⩾ 15 letters was 18.1% in sham, 44.8% in 0.3 mg (P < 0.001) and 39.2% in 0.5 mg ranibizumab (P < 0.001) groups. In RIDE, 12.3% of sham patients, 33.6% of 0.3 mg patients (P < 0.001) and 45.7% of 0.5 mg ranibizumab patients (P < 0.0001) gained ⩾ 15 letters. RISE and RIDE studies demonstrated that monthly ranibizumab achieved better improvements in visual acuity than PRN. The FDA approved ranibizumab for the DME treatment based on the satisfactory outcomes of RISE and RIDE. At 36 mo, the percentage of patients gaining ⩾ 15 letters was 22.0% in sham, 51.2% in 0.3 mg (P < 0.001) and 41.6% in 0.5 mg ranibizumab (P < 0.001) groups in RISE, and 19.2%, 36.8% (P < 0.001) and 40.2% (P < 0.001), respectively, in RIDE. These data revealed that the BCVA improvement at month 24 was sustained through month 36[32].

The RESTORE study compared the mean BCVA change in the ranibizumab 0.5 mg monotherapy or combined laser therapy with the laser alone therapy over 12 mo in 345 DME patients[33]. Both ranibizumab groups received three monthly injections followed by PNR injections through the primary end point (month 12). The mean BCVA improvement was 6.1 letters in the ranibizumab monotherapy group, 5.9 letters in the combination group and 0.8 letters in the laser monotherapy group. The percentage of patients who

gained ⩾ 15 letters at month 12 was 26, 27, and 9 for all groups, respectively. At 2 years, the mean BCVA gain observed at month 12 was maintained in the ranibizumab and combined laser groups (7.9 and 6.7 letters, respectively). In the laser alone group, the mean BCVA was improved from month 12 to 24 (5.4 letters) with an average of 4.1 ranibizumab injections[34]. The 3-year results have also been published[35]. The mean BCVA improvement was 8.0 letters in the ranibizumab monotherapy group, 6.7 letters in the combination group with the mean injection numbers of 6.8 and 6.0, respectively. In the laser only group, the mean BCVA improvement was 6.0 letters with a mean of 6.5 ranibizumab injections from month 12 to 36. They suggested that ranibizumab achieves improving and maintaining BCVA with a progressively decreasing number of injections over 3 years

Aflibercept (EYLEA)

Different from ranibizumab and bevacizumab, aflibercept combines the domains of VEGF receptor (VEGFR-1 and VEGFR-2 receptors) to the FC segment of human immunoglobulin G1. It has the highest affinity to all VEGF-A isoforms among anti-VEGF agents. In addition it binds the other VEGF molecules such as placental growth factors 1 and 2 which have been reported to cause an increased vascular permeability[36]. Its efficacy and safety have been evaluated in patients with DME, AMD and retinal vein occlusions. The European Union has recently approved aflibercept for treatments of exudative AMD and retinal vein occlusion and FDA approved for DME treatment.

The DA VINCI is a multicenter, randomized clinical trial comparing the efficacy of aflibercept with laser photocoagulation in DME patients[37,38]. In this study, patients were randomly divided into five aflibercept application groups: 0.5 mg monthly, 2 mg monthly, 2 mg every 8 wk, 2 mg if necessary following 3 initial monthly injections or macular laser treatment. At 24 wk, the increase in BCVA was from 8.5 to 11.4 letters in aflibercept groups and 2.5 letters in the laser group. The BCVA improvement at 52 wk ranged from 9.7 to 12 letters and 1.3 letters, respectively. Regarding the decrease in CFT, it ranged from -165.4 to 227.4 μm in the aflibercept groups and 227.4 to 58.4 μm in the laser groups.

VISTA (DME) and VIVID (DME) were two double-masked, randomized, phase 3 trials comparing the efficacy of 2 mg aflibercept every 4 wk, 2 mg every 8 wk following the 5 incipient monthly doses, with macular laser photocoagulation[39]. At the first year of VISTA, the mean BCVA improvement was 12.5, 10.7 and 0.2 letters, respectively (P < 0.001). These were 10.5, 10.7 and 1.2 letters, respectively (P < 0.001) in the first year of VIVID. The percentages of patients gaining ⩾ 15 letters were 41.6%, 31.1% and 7.8%, respectively (P < 0.001), in VISTA, and 32.4%, 33.3% and 9.1%, respectively (P < 0.001), in VIVID. Regarding the mean CFT decrease, these were 185.9, 183.1 and 73.3 μm, respectively (P < 0.001), in VISTA, and 195.0, 192.4 and 66.2 μm, respectively (P < 0.001), in VIVID. In conclusion, aflibercept groups achieved better functional and anatomic outcomes at the first year compared to the laser group. However, these were similar between the 4 wk and 8 wk injection groups. After two years of VIVID, the mean BCVA improvement for 2 mg aflibercept every 4 wk and 2 mg every 8 wk was 11.4 and 9.4 letters (P < 0.001), respectively, however, it was 0.7 letters for the laser photocoagulation group. Additionally, the percentage of patients gaining ⩾ 15 letters was 38.2% and 31.1% in the 2 mg aflibercept every 4 wk and 2 mg every 8 wk groups, respectively (P < 0.001) compared to the laser photocoagulation group with a percentage of 12.1. These results demonstrated that the improvement in BCVA resumes after two years.

Protocol T, phase 3 study sponsored by the DRCR will compare the safety and efficacy of intravitreal aflibercept (2.0 mg), bevacizumab (1.25 mg) and ranibizumab (0.5 mg) for DME in 660 patients recruited from different clinical centers in the United States. According to the protocol-specified algorithm, the drugs were injected every 4 wk. The primary outcome in this study is to evaluate the changes in BCVA at month 12. At last visit, the mean BCVA improvement score (range, 0 to 100, and a score of 85 is approximately 20/20) was 13.3 with aflibercept, 9.7 with bevacizumab, and 11.2 with ranibizumab. The BCVA improvement was better in aflibercept group (P < 0.001 for bevacizumab and 0.03 for ranibizumab); however, these were not clinically significant because these differences were due to the eyes with worse baseline BCVA (P < 0.001 for interaction). There were no differences in BCVA among the study groups if the baseline visual loss is mild, however, better improvement was achieved by aflibercept at worse initial BCVA[40].

Bevacizumab (avastin)

Bevacizumab is a full-size, humanized, recombinant monoclonal immunoglobulin G which combines all VEGF A isoforms. It is approved by the FDA for colorectal cancer treatment; however, its usage for ocular diseases is off-label. It is widely used for DME treatment due to its favorable cost and availability[6].

DRCR.net is the first study to suggest that bevacizumab warrants phase 3 evaluation for DME treatment[41]. This randomized study evaluated 121 eyes with DME over 12-wk follow-up (safety data are reported for 24 wk). Five treatment groups were studied: (1) focal photocoagulation; (2) 1.25 mg of bevacizumab administrated at 0 and 6 wk; (3) 2.5 mg of bevacizumab administrated at 0 and 6 wk; (4) 1.25 mg of bevacizumab at baseline plus sham injection at 6 wk; and (5) 1.25 mg of bevacizumab at 0 and 6 wk plus focal photocoagulation at 3 wk. Sixty-nine percent of the study eyes had previous DME treatment. BCVA

was significantly improved in the groups receiving two bevacizumab injections compared to the laser group, and this was continued through the 12-wk follow-up period. The increase in BCVA was 7 letters in the 1.25 mg group and 8 letters in the 2.5 mg group at week 9 (following the second injection). Similar to BCVA, these injection groups showed a greater improvement in CFT compared to others with a similar trend in CFT during follow-up. The CFT results did not show any significant difference between the 1.25 and 2.5 mg groups. The results did not show any difference between the single injection group and the photocoagulation group. The laser and bevacizumab combination group showed similar results with the laser-only group. The BCVA results suggested a worsening trend in these two groups different from the two bevacizumab injections groups. In summary, DRCR.net trial revealed that bevacizumab is a favorable agent for treatment of DME in primary cases and also in previously treated DME eyes. This trial identified two trends: (1) Greater improvement is achieved in the primarily treated eyes (P = 0.04) than the refractory eyes; and (2) The initial subretinal fluid may be associated with a greater improvement in BCVA (P = 0.06).

BOLT study is a prospective study comparing bevacizumab treatment with laser in eyes with persistent DME[42]. In this study 80 eyes were randomly assigned into two groups: (1) bevacizumab group (injections applied every 6 wk, with a minimum of 3 and a maximum of 9 injections); and (2) photocoagulation group (performed at 4 mo and a minimum of 1 and a maximum of 4 sessions). After 1 year, the BCVA and CFT results showed greater improvements in the bevacizumab group than in the laser group. After 2 years, the mean BCVA improvement was 9 letters in the bevacizumab and 2.5 letters in laser groups, and 45% of bevacizumab-treated patients had gained 10 or more letters, which was achieved in 7% of the laser group. In addition CFT was significantly decreased in both groups at 2-year follow-up. This study identified two trends: (1) The patients with better baseline BCVA needed fewer injections; and (2) The eyes with subretinal fluid required more injections compared to eyes with diffuse and cystoid edema.

Ahmadieh *et al*[43] performed a randomized study including 115 eyes with DME. Patients were assigned into three groups: bevacizumab-only group (three 1.25 mg bevacizumab injections every 6 wk), IVTA/bevacizumab combination group (additional injection of 2 mg of triamcinolone at the baseline visit only), and placebo group. The first two groups achieved higher improvement in BCVA compared to placebo only with the exception of the bevacizumab monotherapy group at the first 6 wk. Regarding the difference between the first two groups, no significant difference was found for BCVA and CFT. Following the final injection, the effect of bevacizumab continued for 12 wk without any obvious trend of thorough worsening in BCVA and CFT over that period.

Faghihi *et al*[44] compared bevacizumab monotherapy with combined bevacizumab/IVTA and laser in a pure group of patients with no treatment history for DME. Patients received intravitreal injections of 1.25 mg bevacizumab and 2 mg triamcinolone at the initial visit only. CFT was significantly decreased in all groups at both 6 and 16 wk. The bevacizumab monotherapy group had better improvement in BCVA and CFT compared to the laser group at 6 wk but not at 16 wk. However, the combination group achieved better BCVA and CFT at both 6 and 16 wk than the laser group.

Soheilian *et al*[45] compared the efficacy of bevacizumab alone and in combination with IVTA and laser therapy in treatment of DME in a randomized study with 2-year follow-up. Totally 150 eyes were assigned into three groups: 1.25 mg bevacizumab, bevacizumab/IVTA, and bevacizumab/IVTA/laser. The bevacizumab group yielded a significant increase in BCVA at month 6, which was decreased after month 24. In addition the mean BCVA increase was greater in the bevacizumab alone group compared to other study groups. The combined IVTA/bevacizumab group also achieved higher BCVA results than the laser group. Regarding the reduction in CFT, no significant differences were found between groups; however, this may probably be related to study protocol such as the 3-mo retreatment intervals, when indicated, or the missing data in 24.6% of the cases at the final follow-up.

Pan-American Collaborative Retina Study Group performed a retrospective study including DME patients treated with 1.25 mg or 2.5 mg bevacizumab injections[46,47]. At 2-year follow-up, the rate of patients who gained 2 or more ETDR lines was 51.8% whereas 44.6% eyes remained stable, and 3.6% eyes decreased 2 or more ETDRS lines of BCVA. At the last visit, the OCT findings demonstrated that CFT decreased from 446.4 ± 154.4 μm to 279.7 ± 80 μm. The comparison between 1.25 mg and 2.5 mg bevacizumab groups did not reveal any significance in BCVA and CFT.

Different from the other published studies, Haritoglou *et al*[48] included bevacizumab treated DME patients unresponsive to previous treatment, and with diffuse chronic edema. The intravitreal 1.25 mg bevacizumab injections were administrated at baseline, and were repeated based on the BCVA or CFT responses. The mean CFT significantly improved from 463 to 374 μm at 6 mo (P < 0.001).

SAFETY

Pegaptanib has been approved by FDA for the management of exudative AMD. Two clinical studies were performed to study the efficacy and safety of pegaptanib in patients with DME. Cunningham *et al*[23] reported a case of endophthalmitis that occurred in 1 of 652 injections [0.15%/injection; *i.e.*, 1/130 (0.8%) pegaptanib subjects]. In addition, pegaptanib did not show any association with severe BCVA impairment. In the phase 2/3 study[24], the pegaptanib and sham groups were comparable regarding the frequency of

drug interruptions, drug adverse events, treatment-related adverse events and serious adverse events. No case of endophthalmitis or retinal detachment was reported in either treatment group. For serious events cerebrovascular accidents (CVA) were rare, occurring in 2 (1.4%) and in 1 (0.7%) subjects in the pegaptanib and sham arms, respectively. Coronary artery disease and angina pectoris each occurred in 2 (1.4%) pegaptanib treated and 1 (0.7%) sham treated subjects, hypertension was noted for 1 subject in each group (0.07% for both), and unstable angina was experienced by 2 pegaptanib treated and no sham-treated subjects.

Recently ranibizumab has been approved by FDA for treatment of DME. Each of the above mentioned trials for ranibizumab also reported safety data. In these trials, the most common ocular adverse effect is endophthalmitis. In the RISE and RIDE studies there were four total cases of endophthalmitis out of 500 patients in the two-year follow-up of the study (0.8%; 1 in RISE with 0.3 mg ranibizumab, 3 in RIDE, 1 from 0.3 mg group and 2 from 0.5 mg group)[31]. The three-year follow-up of the DRCR study reported a total of 3 cases of endophthalmitis out of 375 (also 0.8%) patients receiving ranibizumab injections, in either the prompt or deferred laser group[29]. The RESTORE study had no cases of endophthalmitis[33]. RESOLVE had 2 cases of endophthalmitis out of 102 injection patients (2%) over the year of the study[27].

The major systemic safety concern with anti-VEGF treatment is thromboembolic events. In the one-year RESTORE study there were 6 arterial thromboembolic events (5.2%) in the ranibizumab (0.5 mg) group, whereas only one such event occurred in the laser group and the laser plus ranibizumab group[33]. The group sizes were similar, and the analysis did not support a statistical difference between ranibizumab treated groups and the laser only group. The one-year RESOLVE study also reported a low incidence of arterial thromboembolic events with no significant difference among treatment groups (3 of 102 in ranibizumab groups, 2 of 49 in sham group)[27]. The three-year follow-up of the DRCR study also reported no significant difference in thromboembolic events in ranibizumab or sham treated groups[29]. In the RISE and RIDE studies, thromboembolic events and deaths were similar between sham and treatment groups[31]. These studies did report that the number of deaths and CVAs were numerically higher in the ranibizumab groups compared to sham groups, with the highest incidences of CVA and death being in the ranibizumab 0.5 mg group. The number of CVAs in the RISE and RIDE studies combined were 4 out of 250 (1.6%), 3 out of 250 (1.2%), and 8 out of 250 (3.2%), in the sham, 0.3 mg, and 0.5 mg groups, respectively. The number of deaths in the combined studies was 3 out of 250 (1.2%), 7 out of 250 (2.8%), and 11 out of 250 (4.4%) in the sham, 0.3 mg, and 0.5 mg groups, respectively.

The largest study evaluating the safety of bevacizumab reported the data from 1173 patients administrated intravitreal bevacizumab and followed for 12 mo[49]. In this retrospective study these following adverse effects were detected: elevated blood pressure in 7 patients, 6 strokes, 5 myocardial infarctions, 5 deaths, bacterial endophthalmitis in 7 patients, tractional retinal detachment in 7 patients, and uveitis in 4 patients. These reported adverse effects were similar to those detected for the other anti-VEGF substances.

The DA VINCI study reported the safety data for aflibercept therapy for DME at one-year follow-up[38]. Similar systemic side effect profile was reported including hypertension (9.7%), cerebral vascular accidents (1.1%), and myocardial infarction (1.1%). The most of ocular side effects were related to intravitreal injection rather than the drug. Serious adverse effects included endophthalmitis (1.1%), uveitis (0.6%), corneal abrasion (0.6%) and retinal tear (0.6%).

Briefly the majority of safety data for anti-VEGF agents come from studies including patients with neovascular AMD; however, the patients with DME tend to be younger, with a high incidence of heart and kidney diseases in addition to the different ocular status. Because the increased rates of neovascularization and fibrous tissue that may lead to contraction and cause additional ocular complications, further safety studies for DME patients are to be necessary.

COST EFFECTIVENESS

To our knowledge, only two cost-effectiveness analyses have evaluated anti-VEGF treatments for DME. Dewan *et al*[50] compared the cost-effectiveness of ranibizumab with that of intravitreal corticosteroids using the data from the DRCRnet study trial and found that ranibizumab met acceptable cost-effectiveness standards relative to intravitreal corticosteroids for phakic patients (those without previous cataract surgery), and intravitreal corticosteroids were the most cost-effective treatment option for pseudophakic patients (those who had undergone cataract surgery). Bevacizumab was not considered in any of their analyses.

Recently Stein *et al*[51] compared the cost-effectiveness of bevacizumab and ranibizumab. They found that intravitreal bevacizumab confers a better value than ranibizumab. They suggest that insurers and health policymakers should consider endorsing the use of intravitreal bevacizumab over other treatment options as first-line therapy for DME, as this may curtail some of the rapidly rising costs of managing patients with this condition.

CONCLUSION

Review of the literature available to date suggests that intravitreal anti-VEGF pharmacotherapy is reasonably safe and effective for the treatment of DME. However, it may be associated with serious complications in spite of the satisfactory improvement in BCVA and macular edema reduction.

Future studies should focus on longer-term safety

and efficacy of anti-VEGF treatment for DME and should evaluate the comparative efficacy of different pharmacologic agents. Future research should also investigate new molecular targets to prevent or delay the progression of DME and novel strategies for sustained intraocular delivery of anti-VEGF agents to reduce the burden, cost, and risks of injections.

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