Anti–Vascular Endothelial Growth Factor Pharmacotherapy for Diabetic Macular Edema

A Report by the American Academy of Ophthalmology

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Objective: To review the evidence regarding the safety and efficacy of current anti–vascular endothelial growth factor (VEGF) pharmacotherapies for the treatment of diabetic macular edema (DME).

Methods: Literature searches last were conducted in September 2011, in PubMed with no date restrictions, limited to articles published in English, and in the Cochrane Library without a language limitation. The combined searches yielded 532 citations, of which 45 were deemed clinically relevant for the authors to review in full text and to assign ratings of level of evidence to each of the selected studies with the guidance of the panel methodologists.

Results: At this time, there are 5 studies that provide level I evidence for intravitreal ranibizumab, alone or in combination with other treatments for DME. There is also 1 study that provides level I evidence for intravitreal pegaptanib sodium for DME. Nine studies reviewed were rated as level II, and 2 additional studies reviewed were graded as level III. Most studies do not provide information about long-term results (i.e., more than 2 years of follow-up) or the comparative efficacy of anti-VEGF pharmacotherapies.

Conclusions: Review of the available literature indicates that anti-VEGF pharmacotherapy, delivered by intravitreal injection, is a safe and effective treatment over 2 years for DME. Further evidence is required to support the long-term safety of these pharmacotherapies and their comparative efficacy.

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The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment is to review the evidence regarding the safety and efficacy of current anti–vascular endothelial growth factor (VEGF) pharmacotherapies for the treatment of diabetic macular edema (DME).

Background

Diabetic retinopathy is the most frequent cause of legal blindness among working-age individuals in developed countries.[1] An estimated 19 million Americans aged 20 years or older have diagnosed or undiagnosed diabetes mellitus.[2] The International Diabetes Federation estimates that 285 million individuals worldwide have diabetes mellitus and that approximately 14% of this group has DME.[3]

Although diabetes mellitus may cause vision loss by several means including cataract formation or proliferative retinopathy, DME is the most frequent cause. Early histologic findings include capillary basement membrane thickening, loss of pericytes, and loss of endothelial cells. Subsequent formation of microaneurysms, breakdown of the blood–retinal barrier, and consequent vascular leakage result in the pathogenesis of macular edema.

The Early Treatment Diabetic Retinopathy Study (ETDRS) group established level I guidelines for treating patients with clinically significant DME with macular laser photocoagulation.[1,4] These clinical laser treatment guidelines were established before the use of adjunctive pharmacologic agents. A growing body of scientific evidence has implicated VEGF in the pathophysiologic features of DME.[5,6]

There are 4 major anti-VEGF agents that have been evaluated in treating DME: pegaptanib sodium (Macugen;

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Table 1. Randomized Study Results (Level I Evidence) of Intravitreal Anti–Vascular Endothelial Growth Factor Therapy (Ranibizumab and Pegaptanib) for Diabetic Macular Edema

Author(s), Year	Purpose	Study Design	No. of Eyes or Patients	Outcomes Measures	Treatment Regimen	Duration of Study	Results
DRCR,[15] 2010 and Elman et al,[16] 2011 (DRCR)	IVR plus prompt or deferred laser or IVT plus prompt laser	Randomized, prospective, multicenter	854 eyes of 691 patients	BCVA; CST	(A) 0.5 mg IVR plus prompt laser; (B) 0.5 mg IVR plus deferred laser (>24 wks); (C) 4 mg IVT plus prompt laser; (D) sham injection plus prompt laser	2 yrs	Mean VA letter improvement at 1 yr: (A) +9±1, $P<0.001$; (B) +9±12, $P<0.001$; (C) +4±13, $P = 0.31$; (D) +3±13. Mean VA letter improvement at 2 yrs compared with (D): (A) +3.7 (95% aCI, −0.4 to +7.7; $P = 0.03$); (B) +5.8 (95% aCI, +1.9 to +9.8; $P<0.001$); (C) −1.5 (95% aCI, −5.5 to +2.4; $P = 0.35$).
Mitchell et al,[17] 2011 (RESTORE)	IVR vs. focal/grid laser vs. combination for DME	Randomized, prospective, multicenter	345 patients	BCVA, foveal thickness	(A) 0.5 mg IVR monthly ×3 then PRN + sham laser; (B) 0.5 mg IVR monthly ×3 then PRN + laser; (C) sham injections + laser	12 mos	VA better for (A) and (B) from mos 1 to 12 compared with (C); 12-mo VA: (A) +6.1 letters, (B) +5.9 letters, (C) +0.8 letters (both $P<0.0001$); BCVA 20/40 or better: (A) 53%, (B) 44.9%, (C) 23.6%. No significant differences between (A) and (B) at 12 mos.
Googe et al,[18] 2011 (DRCR)	IVR or IVT in eyes receiving focal/grid laser for DME and PRP at 14 wks	Randomized, prospective, multicenter	345 eyes	BCVA, CRT	(A) Sham injection; (B) 0.5 mg IVR at baseline and 4 wks; (C) 4 mg IVT at baseline and sham at 4 wks. All eyes received focal/grid laser for DME and PRP for PDR.	14 wks	Mean changes in BCVA better in (B) (+1±11; $P<0.001$) and (C) (+2±11; $P<0.001$) as compared with (A) (−4±14). The differences were not maintained at 56 wks.
RISE Trial,[19] 2012	IVR for DME	Phase III, randomized, sham-controlled, multicenter	377 patients	BCVA	(A) 0.3mg IVR; (B) 0.5 mg IVR; (C) sham injection. All given monthly injections ×24 mos and with rescue laser available at 3 mos.	2 yrs	Improvement of ≥15 letters at 2 yrs: (A) 44.8% (56/125), (B) 39.2% (49/125), and (C) 18.1% (23/127). Statistically significant for both (A) and (B) compared with (C) at $P<0.0001$ and $P<0.0002$, respectively.
RIDE Trial,[19] 2012	IVR for DME	Phase III, randomized, sham-controlled, multicenter	382 patients	BCVA	(A) 0.3 mg IVR; (B) 0.5 mg IVR; (C) sham injection. All given monthly injections ×24 mos and with rescue laser available at 3 mos.	2 yrs	Improvement of ≥15 letters at 2 yrs: (A) 33.6% (42/125), (B) 45.7% (58/127), and (C) 12.3% (16/130). Statistically significant for both (A) and (B) compared with (C) at $P<0.0001$.

(*Continued*)

Table 1. (Continued.)

Author(s), Year	Purpose	Study Design	No. of Eyes or Patients	Outcomes Measures	Treatment Regimen	Duration of Study	Results
Sultan,[20] 2011	IVP for DME	Phase II/III randomized, sham-controlled, multicenter	260 patients	BCVA, CRT	(A) 0.3 mg IVP or (B) sham injections at baseline and every 6 wks in yr 1 and focal/grid laser beginning at wk 18. In yr 2, (A) 0.3 mg IVP or (B) sham up to every 6 wks PRN.	2 yrs	Improvement of ≥10 letters at 54 wks: (A) 36.8% and (B) 19.7% ($P = 0.0047$). BCVA letters gained at wk 102: (A) 6.1 letters and (B) 1.3 letters ($P<0.01$). No significant difference in CRT decrease at 54 and 102 wks between (A) and (B).

aCI = confidence interval adjusted for multiple comparison; BCVA = best-corrected visual acuity; CRT = central retinal thickness; CST = central subfield thickness; DME = diabetic macular edema; DRCR = Diabetic Retinopathy Clinical Research Network; IVB = intravitreal bevacizumab; IVP = intravitreal pegaptanib; IVR = intravitreal ranibizumab; IVT = intravitreal triamcinolone; logMAR = logarithm of minimum angle of resolution; LPC = laser photocoagulation; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; VA = visual acuity.

[OSI] Eyetech, New York, NY), ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA), bevacizumab intravitreal injection (Avastin; Genentech, Inc., South San Francisco, CA), and VEGF Trap-Eye (VTE; aflibercept and Eylea; Regeneron Pharmaceuticals, Inc., Tarrytown, NY, and Bayer Healthcare Pharmaceuticals, Berlin, Germany), although none currently are approved by the United States Food and Drug Administration (FDA) for this indication.

Pegaptanib sodium was approved by the FDA in December 2004 for the treatment of all subtypes of neovascular age-related macular degeneration (AMD)[7] and is a selective VEGF antagonist that binds to the 165 isoform of VEGF.

Ranibizumab was approved by the FDA in June 2006 for the treatment of all subtypes of neovascular AMD and was approved in 2010 for the treatment of macular edema associated with retinal vein occlusion.[8,9] Ranibizumab is a recombinant humanized immunoglobulin G1 κ isotype therapeutic antibody fragment that binds to and inhibits the biologic activity of all isoforms of human VEGF-A.

Bevacizumab is a full-length monoclonal antibody that also binds all isoforms of VEGF-A. It is approved by the FDA for intravenous use in the treatment of metastatic colorectal cancer, non–small-cell lung cancer, metastatic renal cell carcinoma, and glioblastoma.[10] Bevacizumab's ocular use is off-label.

VEGF Trap-Eye, also known as aflibercept, is the most recent anti-VEGF agent approved by the FDA, in 2011, for the treatment of neovascular AMD.[11] VEGF Trap-Eye is a 115-kDa recombinant fusion protein consisting of the VEGF binding domains of the human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin G1. VEGF Trap-Eye competitively inhibits VEGF and binds placental growth factors 1 and 2.

Resource Requirements

Wholesale prices of the medications range from $1950 per dose for ranibizumab, $1850 per dose for VEGF-Trap Eye, and $995 per dose for pegaptanib, to less than $50 per dose for bevacizumab when compounded for intravitreal use.[12,13]

Question for Assessment

The focus of this assessment is to address the following question: Are the various anti-VEGF pharmacotherapies safe and effective for treating DME?

Description of Evidence

Literature searches last were conducted in September 2011 in PubMed with no date restrictions and limited to studies published in English and in the Cochrane Library without a language limitation. The search strategy used the MeSH term *diabetic retinopathy* and the text words *bevacizumab*, *Avastin*, *ranibizumab*, *Lucentis*, *VEGF Trap Eye*, *aflibercept*, *Eylea*, *pegaptanib*, *Macugen*, *vascular endothelial growth factor*, *VEGF*, *diabetic eye disease*, *diabetic retinopathy*, *diabetic macular edema*, *neovascularization*, *retina*, and *choroid*. The combined searches yielded 532 citations. The panel deemed 45 studies sufficiently clinically relevant to review in full text and assigned ratings of level of evidence to each of the selected articles with the guidance of the panel methodologists. Surveillance of the literature identified one additional study.

The rating scale is based on that developed by the British Centre for Evidence-Based Medicine.[14] A level I rating was assigned to well-designed and well-conducted randomized clinical trials, a level II rating was assigned to well-designed case-control and cohort studies and lower-quality randomized studies, and a level III rating was assigned to case series, case reports, and lower-quality cohort and case-control studies. Of the studies rated and ultimately analyzed in this review, 6 studies were rated as demonstrating level I evidence and 9 studies were rated as demonstrating level II evidence. The remaining 2 studies reviewed were rated as demonstrating level III evidence.

Table 2. Randomized Study Results (Level II Evidence) of Pegaptanib, Bevacizumab, and Ranibizumab for Diabetic Macular Edema

Author, Year	Purpose	Study Design	No. of Eyes or Patients	Outcomes Measures	Treatment Regimen	Duration of Study	Results
Macugen Diabetic Retinopathy Study Group,[25] 2005	PEG for DME	Phase II randomized, double-masked, dose-ranging, controlled	172 patients	BCVA; CRT	(A) 0.3 mg PEG, or (B) sham at baseline, wk 6 and wk 12; additional injections or focal LPC as needed for an additional 18 wks	36 wks	Mean VA at wk 36: (A) 20/50 and (B) 20/63 ($P = 0.04$). Ten letters gained: (A) 34% and (B) 10% ($P = 0.003$). CRT at wk 36: (A) −68 μm and (B) +4 μm ($P = 0.02$). PEG doses of 0.3 mg, 1 mg, and 3 mg all well tolerated.
Diabetic Retinopathy Clinical Research Network,[26] 2007	IVB for DME	Randomized, prospective	121 patients	CST, VA	(A) Focal LPC or (B) IVB 1.25 mg at baseline and 6 wks or (C) 2.5 mg IVB at baseline and 6 wks or (D) 1.25 IVB at baseline and sham at 6 wks or (E) 1.25 IVB at baseline and 6 wks with focal LPC at 3 wks	24 wks	Baseline CST: 411 μm; at 3 wks, CST reduction greater in (B) and (C) than in (A); CST reduced >11% at 3 wks in 43% of IVB-treated eyes and 28% of LPC-treated eyes, and at 6 wks in 37% of IVB-treated eyes and 50% of LPC-treated eyes. Mean 12-wk VA improvement in (B) and (C) of 1 line better than (A). No significant short-term benefit combining IVB and laser.
Soheilian et al,[23,24] 2007 and 2009	IVB or IVB/IVT vs. LPC for DME	Randomized, prospective	150 eyes of 129 patients	BCVA	(A) 1.25 mg IVB, or (B) 1.25 mg IVB +2 mg IVT, or (C) focal or modified grid LPC	24 wks	VA better for (A) and (B) at 6 and 12 wks; 26-wk VA: (A) −0.28±0.25, (B) −0.04±0.33, and (C) +0.01±0.27 logMAR ($P = 0.053$).
Lam et al,[28] 2009	IVB for DME	Prospective, randomized	52 patients	BCVA; foveal thickness	(A) 1.25 mg IVB or (B) 2.5 mg IVB	6 mos	BCVA at 6 mos: (A) improvement from baseline (0.63 logMAR) to 0.52 logMAR; (B) improvement from baseline (0.60) to 0.47; difference between A and B, $P>0.56$; significant reductions in foveal thickness in both groups ($P<0.013$).
Solaiman et al,[27] 2011	IVB vs. focal/grid laser vs. combination for DME	Prospective, randomized	62 eyes of 48 patients	BCVA; foveal thickness	(A) Focal/grid laser (B) 1.25 mg IVB (C) 1.25 mg IVB at baseline and focal/grid laser at 3 wks	6 mos	Mean CRT reduction at 1 mo: (A) 50 μm, (B) 151 μm, and (C) 110 μm. $P\leq0.05$ for (B) and (C) only. BCVA improvement only in (B) and (C) at 1 mo ($P<0.05$). Mean CRT reduction at 6 mos only significant in (C) ($P<0.05$), and no significant change in BCVA at 6 mos between groups.
Rajendram et al,[29] 2012 (BOLT)	IVB vs. focal/grid laser for DME	Prospective, randomized	80 patients	BCVA; foveal thickness	(A) Focal/grid laser or (B) IVB 1.25 mg at baseline, 6 and 12 wks, then as needed	24 mos	Mean gains in BCVA at 24 mos: (A) +2.5 letters; (B) +9 letters ($P = 0.005$). Mean change in CRT at 24 mos; (A) -118 μm; (B) -146 μm.

(*Continued*)

Table 2. (Continued.)

Author, Year	Purpose	Study Design	No. of Eyes or Patients	Outcomes Measures	Treatment Regimen	Duration of Study	Results
Nguyen et al,[21,39] 2009 and 2010 (READ-2)	IVR vs. focal/grid laser vs. combination for DME	Prospective, randomized, interventional, multicenter	126 patients	BCVA; foveal thickness	(A) 0.5 mg IVR at baseline, 1, 3, and 5 mos or (B) focal/grid laser at baseline and 3 mos or (C) combination 0.5 mg IVR and laser at baseline and 3 mos. At 6 mos, all subjects could be treated with IVR if retreatment criteria met.	6 and 24 mos	Mean gains in BCVA at 6 mos: (A) +7.24 letters ($P = 0.01$); (B) −0.43 letters; (C) +3.80 letters. At 24 mos: (A) +7.4 letters, (B) +5.1 letters, (C) +6.8 letters. Improvement of 3 lines or more at 6 mos: (A) 22%; (B) 0% ($P = 0.002$); (C) 8%. At 24 mos: 24% of patients, (B) 18% of patients, and (C) 26% of patients. Excess foveal thickness reduction at 6 mos: (A) 50%; (B) 33%; (C) 45%. Percentage of patients with CST<250 μm at 24 mos: (A) 36%; (B) 47%; (C) 68%. BCVA 20/40 or better at 24 mos: (A) 45%, (B) 44%, and (C) 35%. IVR benefit for 2 yrs, and when combined with focal/grid laser amount of edema and frequency of IVR reduced.
Massin et al,[22] 2010 (RESOLVE)	IVR for DME	Phase II, multicenter, randomized, prospective	151 patients	BCVA, CRT	(A) 0.3 mg or 0.5 mg IVR monthly ×3 mos then as needed (dose-doubling allowed after 1 mo); (B) sham injection monthly ×3 mos then as needed (as-needed rescue LPC in both groups).	1 yr	Mo 12 mean±SD BCVA change: (A) 10.3±9.1 letters, (B) −1.4±14.2 letters; $P<0.0001$. Gain ≥10 letters: (A) 60.8%, (B) 18.4% ($P<0.0001$). Mean change in CRT: (A) −194.2 μm, (B) −48.4 μm ($P<0.0001$).
Do et al,[30] 2011	VTE vs. focal/grid laser for DME	Phase II, multicenter, randomized, prospective	221 patients	BCVA, CRT	(A) 0.5 mg VTE every 4 wks; (B) 2 mg VTE every 4 wks; (C) 2 mg VTE every 4 wks for 3 mos, then every 8 wks; (D) 2 mg VTE every 4 wks for 3 mos, then PRN; (E) focal/grid laser.	24 wks	The change in baseline BCVA at 24 wks was greater in each (A), (B), (C), and (D) as compared with (E) ($P = 0.0085$). Study not powered to detect differences between VTE groups. Reduction in CRT in each (A), (B), (C), and (D) was significant compared with (E) at 24 wks ($P = 0.0066$).

BCVA = best-corrected visual acuity; CRT = central retinal thickness; CST = central subfield thickness; DME = diabetic macular edema; IVB = intravitreal bevacizumab; IVR = intravitreal ranibizumab; IVT = intravitreal triamcinolone; logMAR = logarithm of minimum angle of resolution; LPC = laser photocoagulation; PEG = pegaptanib; SD = standard deviation; VA = visual acuity; VTE = VEGF-Trap Eye.

Published Results

Multiple level I studies (Diabetic Retinopathy Clinical Research [DRCR] Network, RESTORE Study,[17] RISE and RIDE Research Group[19]) support the use of anti-VEGF agents in the treatment of DME. These level I studies[15–19] reported significantly better visual outcomes at 1 to 2 years for patients with DME who were treated with ranibizumab alone or in combination with other treatments. A randomized level I study[20] of intravitreal pegaptanib sodium compared with sham injection reported better visual acuity outcomes at years 1 and 2 for pegaptanib-treated patients.

One level II study[21] reported significantly better visual outcomes at 6 months for patients with DME who were treated with intravitreal ranibizumab compared with focal/grid laser treatment. Another level II study[22] showed efficacy of intravitreal ranibizumab for DME at varying doses with 12 months of follow-up. Six level II studies[23–29] (references 22 and 23 relate to the same study) found some effect of intravitreal pegaptanib sodium or intravitreal bevacizumab in improving visual acuity outcomes, reducing leakage on fluorescein angiography, reducing central retinal thickness on optical coherence tomography, or a combination thereof. A single level II study[30] demonstrated better visual and optical coherence tomography outcomes for patients treated with VTE at different doses and dosing regimens compared with focal/grid laser for the treatment of DME over 24 weeks of follow-up.

Results from the 6 level I reports of anti-VEGF agents for DME are listed in Table 1. Results from level II reports on anti-VEGF agents for DME are listed in Table 2. Table 3 displays results of level III case series of intravitreal bevacizumab for DME.

Pegaptanib

Positive results from a phase 3, multicenter, randomized study (n = 260) of intravitreal pegaptanib compared with sham injection for DME have been published (Table 1).[20] This clinical trial compared 0.3 mg of intravitreal pegaptanib every 6 weeks with a sham injection; patients could receive macular laser treatment in the study after week 18 based on ETDRS criteria. No safety issues were identified in this study, and pegaptanib was superior to sham injection with respect to 2-line visual acuity gains at month 12, 37% (pegaptanib) versus 20% (sham; $P = 0.0047$). Mean best-corrected visual acuity (BCVA) at month 12 was +5.1 letters (pegaptanib) compared with +1.2 letters (sham; $P<0.05$), and the mean BCVA at month 24 was +6.1 letters (pegaptanib) compared with 1.3 letters (sham; $P<0.01$).

Bevacizumab

Bevacizumab is used off-label to treat DME. A short-term level II study by Soheilian et al[23,24] (the publications are related to the same study; Table 2) evaluating the visual acuity results of intravitreal bevacizumab alone or combined with intravitreal triamcinolone versus laser photocoagulation for DME found that patients who received bevacizumab injections (n = 37) had significantly better visual acuity outcomes at 12 weeks compared with patients who received laser photocoagulation.[24] In a follow-up study,[24] the mean visual acuity (logarithm of the minimum angle of resolution) for the intravitreal bevacizumab-only group was significantly better than baseline at 24 weeks.

The DRCR Network[26] conducted a phase II randomized exploratory clinical trial of the short-term effect of intravitreal bevacizumab for DME (Table 2). The patients in this level II study (n = 121) were randomized into the following 4 groups: group A, focal laser photocoagulation at baseline (n = 19); group B, injection of intravitreal bevacizumab 1.25 mg at baseline and 6 weeks (n = 22); group C, injection of intravitreal bevacizumab 2.5 mg at baseline and 6 weeks (n = 24); group D, injection of intravitreal bevacizumab 1.25 mg at baseline and sham injection at 6 weeks (n = 22); and group E, injection of intravitreal bevacizumab 1.25 mg at baseline and 6 weeks and focal laser photocoagulation at 3 weeks (n = 22). Groups B and C had a larger reduction in retinal thickness as seen on optical coherence tomography at 3 weeks and an approximately 1-line improvement in vision at 12 weeks when compared with group A. The combination of bevacizumab with laser photocoagulation had no short-term benefit in this study.

A more recent level II study by Solaiman et al[27] (Table 2) randomized 62 eyes of 48 patients to either focal/grid laser (group A), 1.25 mg intravitreal bevacizumab (group B), or 1.25 mg intravitreal bevacizumab at baseline and focal/grid laser at 3 weeks (group C). There was a significant reduction in mean central retinal thickness of groups B and C compared with group A and a corresponding short-term improvement in BCVA.

A level III study by the Pan-American Collaborative Retina Study Group[31] reported 2-year results from a retrospective comparative case series of intravitreal bevacizumab (1.25 or 2.5 mg) for DME (Table 3). Mean BCVA at 24 months improved significantly from baseline vision for both doses ($P<0.0001$). In the 1.25-mg group, mean central macular thickness decreased from 466.5 ± 145.2 μm at baseline to 286.6 ± 81.5 μm at 24 months ($P<0.0001$), and similar results were observed in the 2.5-mg group.

Haritoglou et al[32] reported on the efficacy of intravitreal injection of 1.25 mg bevacizumab for patients with persistent diffuse DME. Mean decrease in retinal thickness at 12 weeks was significant, from 501 ± 163 μm at baseline to 377 ± 117 μm ($P = 0.001$).

Most recently the level II Bevacizumab or Laser Therapy (BOLT) study (Table 2) reported 2-year results comparing intravitreal bevacizumab 1.25 mg versus focal macular laser treatment for DME in 80 subjects.[29] Median gain in BCVA was superior for intravitreal bevacizumab (+9 letters; median, 13 treatments) compared with macular laser treatment (+2.5 letters; median, 4 laser treatments; $P = 0.005$). Mean central macular thickness reduction was slightly greater in the intravitreal bevacizumab group at 24 months (-146 μm) versus the macular laser treatment group (-118 μm) but was not statistically different ($P = 0.62$). This study provides

Table 3. Case Series Results (Level III Evidence) of Bevacizumab for Diabetic Macular Edema

Author, Year	Purpose	Study Design	No. of Eyes of Patients	Outcomes Measures	Treatment Regimen	Results
Arevalo et al,[31] 2009	IVB for diffuse DME	Retrospective, multicenter, interventional case series	139 eyes	BCVA, CST	(A) IVB 1.25 mg or (B) IVB 2.5 mg	BCVA improvement at 24 mos: (A) from baseline (0.88 logMAR) to 0.57 logMAR ($P<0.0001$); (B) from baseline (0.92) to 0.78 ($P<0.0001$). CST decrease: (A) from baseline (466.5±145.2 μm) to 286.6±81.5 μm ($P<0.0001$).
Haritoglou et al,[32] 2006	IVB for persistent diffuse DME	Prospective, consecutive, noncomparative case series	51 eyes of 51 patients	VA, CRT	1.25 mg IVB	Mean baseline VA: 0.86±0.38 logMAR of Snellen letters; mean baseline CRT: 501±163 μm. VA improvement at 6 wks: 0.75±0.37 logMAR of Snellen letters ($P = 0.001$) with some regression at 12 wks. CRT at 12 wks: 377±117 μm ($P = 0.001$).

BCVA = best-corrected visual acuity; CRT = central retinal thickness; CST = central subfield thickness; DME = diabetic macular edema; IVB = intravitreal bevacizumab; logMAR = logarithm of minimum angle of resolution; VA = visual acuity.

evidence for longer term use of intravitreal bevacizumab injections for DME.

Ranibizumab

Multiple level I studies (DRCR, RESTORE, RISE, RIDE) have demonstrated the efficacy of intravitreal ranibizumab for the treatment of DME. Level I data from the DRCR Network[15] showed that patients treated with 0.5 mg ranibizumab plus prompt laser (n = 187) or deferred laser (≥24 weeks; n = 188) had significantly better visual acuity outcomes at the 1-year mark than those treated with sham injection plus prompt laser (n = 293). Mean visual acuity improvement was significantly better at 1 year in the ranibizumab plus prompt laser group (+9±12; $P<0.001$) and the ranibizumab plus deferred laser group (+9±12; $P<0.001$) compared with sham plus prompt laser (+3±13). The 2-year results demonstrated similar findings.[16]

The RESTORE trial[17] randomized 345 patients to receive either 0.5 mg ranibizumab monthly for 3 months then as needed plus sham laser (group A), 0.5 mg ranibizumab monthly for 3 months then as needed plus laser (group B), or sham injections plus laser (group C). They reported a 12-month visual acuity improvement of 6.1 ETDRS letters with ranibizumab alone (group A), 5.9 letters with ranibizumab combined with laser (group B), and 0.8 letters with laser alone (group C). The difference between both groups A and B compared with groups C was statistically significant ($P<0.0001$). Mean central retinal thickness also decreased significantly in both ranibizumab groups compared with laser alone (group A, −118.7 μm; group B, −128.3 μm; group C, +61.3 μm; $P<0.001$ for both group A and group B).

The RISE and RIDE trials are identical, parallel confirmatory studies designed to support the indication for ranibizumab for the treatment of DME. The RISE trial[19] enrolled 377 patients with DME and randomly assigned them to receive monthly injections of either 0.3 mg ranibizumab (group A), 0.5 mg ranibizumab (group B), or sham injection (group C). At 3 months, rescue laser was made available to all patients. At 24 months, 44.8% of patients (56/125) who received 0.3 mg ranibizumab and 39.2% of patients (49/125) who received 0.5 mg ranibizumab were able to read at least 15 more letters than at baseline compared with 18.1% of patients (23/127) who received sham injections. The RIDE trial[19] enrolled 382 patients with treatment groups identical to those in the RISE trial. The presented data demonstrate that at 24 months, 33.6% of patients (42/125) who received 0.3 mg ranibizumab and 45.7% of patients (58/127) who received 0.5 mg ranibizumab were able to read at least 15 more letters than at baseline compared with 12.3% of patients (16/130) who received sham injections.

In a short-term 6-month level II study,[21] the Ranibizumab for Edema of the Macula in Diabetes (READ-2) study, 126 patients with DME were randomized 1:1:1 to receive 0.5 mg of ranibizumab at baseline and months 1, 3, and 5 (group 1), focal/grid laser at baseline and month 3 if needed (group 2) or a combination of 0.5 mg ranibizumab and focal/grid laser at baseline and month 3 (group 3). At 6 months, mean ETDRS BCVA was significantly greater in group 1 (+7.24 letters; $P = 0.01$) compared with group 2 (−0.43 letters). Results from group 3 (+3.80 letters) were not statistically different those of groups 1 or 2. Improvement in visual acuity of 3 lines or more was observed in 22% in group 1, compared with 0% in group 2 ($P = 0.002$) and 8% in group 3.

In the level II RESOLVE trial,[22] 151 patients were randomized to 0.3 mg or 0.5 mg intravitreal ranibizumab monthly for 3 months, with dose-doubling allowed after 1 month (group A), versus sham injection monthly for 3 months then as needed (group B). Both groups were eligible to receive rescue grid laser at 1 year. The BCVA improved by 10.3±9.1 letters in the ranibizumab group versus −1.4±14.2 letters in the sham group ($P<0.0001$). Patients with 10-letter gains also were significantly greater in the ranibizumab group, with 60.8% versus 18.4% ($P<0.0001$), and with a corresponding reduction in central retinal thickness of −194.2 μm versus an increase of 48.4 μm ($P<0.0001$). In addition, a larger proportion of patients

in the sham group received rescue laser photocoagulation compared with the ranibizumab group (34.7% vs. 4.9%).

VEGF Trap-Eye

The phase II DA VINCI (DME and VEGF Trap-Eye: INvestigation of Clinical Impact) trial[30] demonstrated the efficacy of VTE compared with macular laser for the treatment of DME. In this level II study, 221 patients with clinically significant DME involving the central macula were enrolled in this prospective, double-masked clinical trial. Patients were randomized to 1 of 5 treatment protocols: group A, 0.5 mg VTE every 4 weeks; group B, 2 mg VTE every 4 weeks; group C, 2 mg VTE every 4 weeks for 3 months, then every 8 weeks; group D, 2 mg VTE every 4 weeks for 3 months, then PRN; and group E, focal/grid laser. At 24 weeks, treatment groups with VTE showed visual acuity benefits between +8.5 and +11.4 ETDRS letters compared with +2.5 letters in the laser group ($P \leq 0.0085$ for each treatment group vs. laser). The mean central macular thickness also was reduced significantly in the groups treated with VTE. Adverse events were reported as consistent with other intravitreal treatment agents.

Safety

Serious ocular adverse effects of intravitreal injections are well known and include uveitis, endophthalmitis, and retinal detachment. From the literature available to date, there seem to be no greater ocular risks to patients with DME receiving intravitreal anti-VEGF injections than other subgroups of patients, but longer-term follow-up is needed. For example, patients with DME typically are younger than patients with AMD and thus may be at greater risk of cataract progression and elevated intraocular pressure after repeated injections.

There are several studies that provide data on the systemic safety of intravitreal anti-VEGF injections, particularly with respect to the treatment of neovascular AMD.[33] Pegaptanib and ranibizumab have been evaluated in prospective, randomized controlled clinical trials as part of the FDA approval process for the treatment of patients with neovascular AMD (although it should be noted that these clinical trials were not powered to detect significant differences among study groups with respect to low-frequency adverse events). For ranibizumab, the combined rate of myocardial infarction and stroke during the first year of the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) trials was higher in the 0.5-mg arm than in controls (2.9% and 1.3%, respectively); these differences were not statistically significant and were not evident at the 2-year follow-up (level I evidence).[34,35] In a phase IIIb study[36] (Safety Assessment of Intravitreous Lucentis for AMD Study, Cohort 1) to evaluate the safety of intravitreal ranibizumab (0.3-mg and 0.5-mg doses) in patients with neovascular AMD, a planned interim analysis at 6 months showed that there was a higher incidence of strokes in the 0.5-mg dose group compared with the 0.3-mg dose group (1.2% vs. 0.3%; $P = 0.02$). The data at 1 year suggested a trend toward a higher incidence of stroke in the 0.5-mg dose group (1.2% vs. 0.7% in the 0.3-mg dose group), although these results are not statistically significant. In the Comparison of Age-Related Macular Degeneration Treatment Trial,[37] the rates of serious systemic adverse effects (death, myocardial infarction, stroke) were similar for patients receiving either bevacizumab or ranibizumab and were in line with previous published studies. In the RISE and RIDE trials, ocular and systemic safety seemed to be consistent with previous ranibizumab phase III studies.[19] From the literature available to date, there seem to be no greater systemic risks to DME patients receiving intravitreal anti-VEGF injections.

Economic and Quality-of-Life Considerations

The relative costs and treatment benefits of anti-VEGF pharmacotherapy and other treatment methods for DME have been compared.[38] The cost in dollars per line of vision saved at 1 year ranged from $1329 to $2246 for bevacizumab, $3749 for intravitreal triamcinolone, $5099 for grid laser, $10 500 for pegaptanib, and $11 372 to $11 609 for ranibizumab. These costs translated to quality-adjusted life years are $2013 to $4160 for bevacizumab, $5862 for grid laser, $6246 for intravitreal triamcinolone, $16 667 for pegaptanib and $19 251 to $23 119 for ranibizumab. This analysis underscores the relatively high cost of treatment despite proven benefit.

Conclusions

Review of the literature available to date suggests that anti-VEGF pharmacotherapy, delivered by intravitreal injection, is reasonably safe and effective for the treatment of DME. The cost of these treatments, however, is relatively high, and further study is required to evaluate the long-term cost-effectiveness of these treatments.

Future Research

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 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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