Publisher: Taylor & Francis

Journal: *Expert Opinion on Biological Therapy*

DOI: 10.1517/14712598.2016.1131265

Treatment Strategies for Refractory Diabetic Macular Edema: Switching Anti-VEGF Treatments, adopting corticosteroid-based treatments, and combination therapy

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Abstract

Introduction: The pathophysiology of diabetic macular edema (DME) is complex, involving vascular endothelial growth factor (VEGF) and other inflammatory mediators. DME is currently treated first-line with intravitreal anti-VEGF treatments, though some cases are refractory to multiple anti-VEGF treatments.

This is the author's manuscript of the article published in final edited form as:
Hussain, R. M., & Ciulla, T. A. (2016). Treatment strategies for refractory diabetic macular edema: switching anti-VEGF treatments, adopting corticosteroid-based treatments, and combination therapy. Expert Opinion on Biological Therapy, 16(3), 365–374. http://doi.org/10.1517/14712598.2016.1131265

Areas Covered: This article examines the evolution of treatment practices for DME, with discussion of the recent studies that guide treatment for refractory cases of DME. A literature search was performed using the following terms: anti-VEGF, DME, aflibercept, bevacizumab, ranibizumab, refractory macular edema, and VEGF.

Expert Opinion: Focal extrafoveal DME may be treated first-line with laser. In patients with center-involving DME and only mild vision loss, consider starting treatment with bevacizumab, especially when cost is an issue, whereas aflibercept may be considered more strongly in patients with moderate visual loss or worse. There are no standard protocols that define "treatment failure," but several studies have reported that switching from bevacizumab to either ranibizumab or aflibercept will result in further reduction of CSFT and improvement in BCVA. Further study with prospective randomized trials is warranted to validate these findings. Switching to intravitreal corticosteroids may be of particular benefit to pseudophakic patients. Anti-VEGF combination with sustained-release corticosteroids also appears promising for refractory DME.

Keywords: aflibercept, Avastin, bevacizumab, dexamethasone, diabetic macular edema, DME, Eylea, fluocinolone acetonide, Iluvien, ranibizumab, Lucentis, Ozurdex, VEGF

1. Introduction

Diabetic macular edema (DME) is a leading cause of blindness in the working-age population of most developed countries [1]. The Wisconsin Epidemiologic Study of Diabetic Retinopathy showed that the ten-year rate of developing DME in the US was 20.1% among Type I diabetics, 25.4% among insulin-dependent Type II diabetics, and

13.9% for non-insulin dependent Type II diabetics [2]. Nearly half of those developing DME will lose two or more lines of visual acuity within two years [3].

Macular laser photocoagulation, which had traditionally been standard treatment for DME since the Early Treatment Diabetic Retinopathy Study (ETDRS), slows the rate of vision loss and helps stabilize vision, but has demonstrated only limited ability to restore lost vision [4]. Intravitreal medications targeted toward vascular endothelial growth factor (VEGF) have become first line therapy in DME patients. These medications bind VEGF, thereby decreasing angiogenesis and vascular permeability, causing regression of diabetic neovascularization and reduction in DME respectively [1, 5]. Several recent clinical trials suggest that these therapies are more effective for DME than laser therapy [6-13].

2. Pathophysiology of DME

Chronic hyperglycemia contributes to alterations in the structural and cellular components of retinal microvasculature. Early on, there is damage to the pericytes that are responsible for regulating capillary perfusion, which results in microaneurysm formation and impaired regulation of retinal blood flow [14]. Damage to endothelial cells that are responsible for maintaining the blood-retinal barrier allows for accumulation of extracellular fluid in the macula. There is also thickening of the capillary basement membrane and increased deposition of extracellular matrix components [1, 14, 15]. Over time, continued retinal microvasculature damage results in capillary nonperfusion and retinal ischemia, resulting in upregulation of angiogenic factors, such as vascular endothelial growth factor (VEGF) [5].

VEGF plays a key role not only in angiogenesis, but also in vascular permeability [16]. There are several different VEGF isoforms due to the alternative splicing and include VEGF-A, VEGF-B, VEGF-C, VEGF-D and VEGF-E, and placental growth factor (PLGF). The actions of VEGF family members are mediated by the activation of tyrosine kinase receptors. The VEGF receptors (VEGFR) have seven immunoglobulin–like loops in their extra cellular domain and a kinase insert region in the intracellular domain. VEGFRs can signal via mitogen-activating protein kinase (MAPK) signaling pathway or through elevation in intracellular calcium concentration in endothelial cell forming the vessel walls [17].

VEGF-A is a critical regulator of ocular angiogenesis and vascular permeability. VEGF-A acts at VEGFR 1 and 2. VEGFR1 (fms-like tyrosine kinase-1) has both positive and negative angiogenic effects; VEGFR2 (fetal liver kinase-1 and kinase insert domain-containing receptor) is the primary mediator of the mitogenic, angiogenic and vascular permeability effects of VEGF-A [16]. VEGF mediates angiogenesis by promoting endothelial cell (EC) migration, proliferation, and survival. VEGF also possesses inflammatory properties through its capacity to mediate microvascular permeability and increase adhesion of leukocytes. VEGF was found to stimulate expression of intracellular adhesion molecule -1 (ICAM-1) and vascular cell adhesion molecule -1 (VCAM-1) [18], thus incorporating the inflammatory cascade, initiating early diabetic retinal leukocyte adhesion and aiding the development of diabetic vasculopathy.

Inflammation plays an important role in the pathogenesis of DME, in which there is upregulation of prostaglandins and other inflammatory mediators, such as tumor

necrosis factor-alpha, cyclooxegenase-2, and interleukin-6, interleukin-8, Pentraxin-3, and Monocyte chemotactic protein-1 (see Table 2). In diabetic patients, leukocytes are more rigid and a higher proportion than usual are activated; increased retinal leukostasis results in capillary non-perfusion, endothelial cell damage, and vascular leakage via generation of toxic superoxide radicals and proteolytic enzymes [19, 20].

3. Bevacizumab for DME

Bevacizumab is a full-length (149 kDa) recombinant humanized monoclonal IgG1 antibody that binds all isoforms of VEGF-A [21]. It was originally approved for the treatment of metastatic colorectal cancer, but was first used off-label in 2005 for the treatment of exudative age-related macular degeneration (AMD). Its off-label use has been expanded to treat macular edema due to venous occlusions, as well as DME. It is the most cost-effective anti-VEGF option [22] and hence the first option considered for many patients. The BOLT study was a randomized prospective clinical trial of 80 patients with center-involving DME who had received at least one prior laser treatment; subjects were randomly assigned to receive either 1.25 mg bevacizumab injections (3 initial injections every 6 weeks with possible further injections guided by an optical coherence tomography (OCT)-based protocol) or additional modified ETDRS macular laser therapy (examination every 4 months with re-treatment as warranted by ETDRS guidelines) [12]. At 12 month follow up, the bevacizumab group had best-corrected visual acuity (BCVA) improve by a median of 8 ETDRS letters, compared to a loss of 0.5 letters in the laser group ($p = 0.0002$). The central subfield thickness (CSFT) improved by a mean of 129 μm, compared to only 68 μm in the laser group. Bevacizumab continued to show superior BCVA and anatomic results compared to laser at 24 month follow up, with the

bevacizumab group showing a mean gain of 8.6 letters versus loss of 0.5 letters for laser, and reduction of CSFT by 146 μm compared to only 118 μm for laser [13].

The Pan-American Collaborative Retina Study Group retrospectively studied the efficacy of 1.25 mg vs 2.5 mg bevacizumab doses for diffuse DME. At 24 month follow up and after a mean of 5.8 (range 1-15) injections, the mean BCVA improved from 20/150 to 20/75 ($p<0.0001$), and mean CSFT decreased by 179 μm ($p<0.0001$) in the 1.25 mg dose group. For the 2.5 mg group, BCVA improved from 20/168 to 20/118 ($p=0.02$) and CSFT improved by 151 μm ($p<0.0001$). No statistically significant differences were found in CSFT or BCVA between the 1.25 and 2.5 mg bevacizumab groups [23].

4. Ranibizumab for DME

Ranibizumab, a smaller (48kDa) recombinant humanized monoclonal IgG1 antibody fragment (Fab), was specifically manufactured for use in the eye (unlike bevacizumab), and inhibits all known isoforms of VEGF-A. This molecule lacks a fragment crystallizable (Fc) region, which allows for faster systemic clearance [24]. Ranibizumab was approved by the U.S. Food & Drug Administration (FDA) for DME in 2012, based on Genentech's Phase III trials, RIDE and RISE [25, 26]. These two identically-designed, parallel, double-masked, three-year clinical trials were sham-treatment controlled for 24 months. A total of 759 patients were randomized into three groups to receive monthly treatment with 0.3 mg ranibizumab (n=250), 0.5 mg ranibizumab (n=252) or sham injection (control group, n=257). Beginning at three months, macular laser rescue treatment was made available to all patients, if needed, based on pre-specified criteria. After month 24, patients in the sham injection group were

eligible to receive monthly injections of 0.5 mg ranibizumab and all patients were followed and dosed monthly for a total of 36 months.

Compared to controls, a significantly greater percentage of ranibizumab-treated patients were able to read at least three additional lines (15 letters) at 24 months (primary endpoint). The number of ETDRS letters gained at 24 months follow up was 12.5, 11.9, and 2.6 in the 0.3 mg ranibizumab, 0.5 mg ranibizumab, and sham groups, respectively (RISE). In RIDE, the number of letters gained was 10.9, 12, and 2.3 in the same order. Both ranibizumab dose groups showed similar reduction in CSFT that was superior to sham: RISE: 251 μm (0.3 mg ranibizumab), 253 μm (0.5 mg ranibizumab), and 133 μm (sham); RIDE: 260 μm (0.3 mg ranibizumab), 271 μm (0.5 mg ranibizumab), and 126 μm (sham).

Patients in the sham group required more rescue laser treatments (1.8) compared to both ranibizumab groups (0.8 each) by 24 month follow up [26] Additionally, in both studies, significantly more patients who received ranibizumab compared with sham injections achieved vision greater than or equal to 20/40 and reported greater improvements in their ability to perform vision-related daily activities such as reading and driving, compared to the sham group, based on composite responses to the 25- item National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25)[27]. The 36-month results indicate that patients in the sham group, who were eligible to cross over to monthly 0.5 mg ranibizumab after 24 months, did not achieve the same degree of VA gains as those patients who were in the ranibizumab group. After 12 months of ranibizumab, the crossover group only gained 2.8 letters compared to 10.6 and 11.1 letters in the 0.3 and 0.5 mg ranibizumab groups, respectively. This suggests that chronic

macular edema may lead to a certain amount of irreversible VA loss, despite the fact that these patients CSFT improved by only 20 μm less than the ranibizumab group [25].

The RESTORE study demonstrated superiority of ranibizumab alone or in combination with laser, compared to using laser monotherapy, as treatment options for DME. At 12 months, CSFT was reduced by 119 μm, 128 μm, and 61 μm in the ranibizumab monotherapy, ranibizumab + laser, and laser monotherapy groups, respectively ($p<0.001$). BCVA improved by 6.1, 5.8, and 0.9 letters in these groups by 12 months, respectively ($p<0.0001$). Visual acuity gains were associated with significant gains on the VFQ-25 scores [28]. Ranibizumab combined with prompt or deferred laser was also found to be superior to laser monotherapy in DRCR.net Protocol I [7].

5. Aflibercept for DME

In 2014, aflibercept (also known as VEGF Trap-EYE) was approved for the treatment of DME. Aflibercept is a recombinant fusion protein that is composed of the second extracellular binding domain from human VEGFR-1 and the third binding domain fromVEGFR-2 fused to the Fc domain of human immunoglobulin G1 molecule; it inhibits VEGF-A, VEGF-B and placental growth factor (PlGF) [21]. Regeneron's Phase 3 VISTA-DME and VIVID-DME studies of 862 patients compared aflibercept 2 mg given monthly (2q4), aflibercept 2 mg given every two months (2q8 after five initial monthly injections), or macular laser photocoagulation (at baseline and then as needed) [29, 30].

In the VISTA 52 week follow up, the 2q4 and 2q8 aflibercept dosing groups gained 12.5 and 10.7 ETDRS letters, respectively, compared to only 0.2 letters in the

laser group ($p<0.0001$). In VIVID, the 2q4 and 2q8 groups gained 10.5 and 10.7 letters versus only 1.2 letters in the laser group ($p<0.0001$). The anatomic reduction in CSFT was similar for both dosing regimens in VISTA: 186 μm (2q4) and 183 μm (2q8) compared to only 73 μm in laser. For VIVID, the difference between aflibercept and laser was even more pronounced, with 2q4 and 2q8 groups reducing CSFT by 195 μm and 192 μm, respectively, compared to only 66 μm for laser. Additional rescue laser was given to fewer eyes in the 2q4 and 2q8 groups (0.7% and 2.6% for VISTA and 4.4 and 8.1% for VIVID) compared to the laser group (31.2% for VISTA and 24.1% VIVID). A greater proportion of eyes in VISTA had previously received anti-VEGF injections (43% vs 9%) [31].

The 100-week VIVID and VISTA results were recently published, and they report sustained superiority of aflibercept over laser. In VIVID, there were 11.5, 11.1, and 0.9 letter gains in the 2q4, 2q8, and laser groups, respectively. In VISTA, there were 11.4, 9.4, and 0.7 letter gains for the same groups [29]. The FDA-approved dosing for aflibercept is 2 mg every 2 months following 5 initial monthly injections. It also may be dosed once per month, but as the studies suggest, additional benefit was limited with this dosing plan. Analysis of eyes with CSFT reduction of <10% by week 12 indicated that these eyes generally underperformed compared to the entire cohort. By week 52, the 2q4, 2q8, and laser groups had gains of 8.2, 10.5, and -2.6 letters in VISTA, and 7.4, 10.9, and 0.8 letters in VIVID. The corresponding gains at week 100 were 6.6, 7.6, and -2.0 letters in VISTA, and 9.6, 8.1 and -0.1 letters in VIVID (Boyer DS, presented at Retina Society, Paris, France, October 8, 2015).

6. Comparing Anti-VEGF Options in DME

While the above mentioned studies show clear cut superiority of anti-VEGF treatments compared to laser for center-involving DME, there are not many large scale prospective studies comparing the efficacy of the anti-VEGFs to one another. On quick glance at the numbers reported in the aforementioned studies, it suggests that aflibercept and ranibizumab may be more effective than bevacizumab at reducing CSFT and improving BCVA. However, there are limitations in comparing numbers between separate studies with different treatment strategies and patient populations, especially given that the BOLT study was much smaller than RISE/RIDE and VIVID/VISTA. It is best to compare the anti-VEGF agents directly in a trial.

This issue was addressed by the National Institutes of Health (NIH) sponsored, Diabetic Retinopathy Clinical Research Network (DRCR.net) comparative effectiveness study in patients with Diabetic Macular Edema (Protocol T). Aflibercept was compared to ranibizumab and bevacizumab for the treatment of DME in this study. Six hundred and sixty patients were randomized to receive either aflibercept 2 mg, bevacizumab 1.25 mg, or ranibizumab 0.3 mg dosed according to a protocol-specified algorithm. Anti-VEGF treatment within 12 months was exclusionary. Patients were treated with focal/grid laser at or after the 24 week visit if: 1) the OCT central subfield thickness was greater than or equal to 250 microns or there was edema that was threatening the fovea and 2) the eye did not improve on OCT or visual acuity from the last two consecutive injections [32].

In DRCR Protocol T, aflibercept demonstrated a significantly greater improvement in mean visual-acuity letter score at 52 weeks compared to both bevacizumab and ranibizumab injection in the subgroups with baseline ETDRS visual

acuity of 20/50 or worse (gain of 13.3, 9.7, and 11.2 letters in each group, respectively; p <0.0001 for aflibercept vs. bevacizumab; p = 0.03 for aflibercept vs. ranibizumab). There was no significant difference in visual acuity between the subgroups with better baseline visual acuity between 20/32 -20/40 (mean improvement of 8.0, 7.5, and 8.3 letters for aflibercept, bevacizumab, and ranibizumab, respectively; p>0.50 for each pairwise comparison). Anatomically, aflibercept and ranibizumab demonstrated a statistically significant greater reduction of CSFT compared to bevacizumab, with values of -169 μm, -147 μm, and -101 μm, respectively (p<0.001 for aflibercept and ranibizumab vs. bevacizumab; p = 0.036 for aflibercept vs. ranibizumab). These results held true regardless of initial baseline BCVA. The median number of injections using the protocol-specified retreatment regimen was one fewer in patients treated with aflibercept (9 injections) compared to bevacizumab and ranibizumab (10 injections each, p =0.045 for overall comparison). Fewer patients in the aflibercept group (37%) received criteria-based macular laser treatments than those treated with bevacizumab (56%) and ranibizumab (46%, p<0.001 for overall comparison) [32]. These results allow one to speculate that either aflibercept or ranibizumab would be of potential benefit for treating persistent DME after trial with bevacizumab, though one must keep in mind that the subjects had not received anti-VEGF injections for at least 12 months prior to the study.

Furthermore, the rates of most ocular and systemic adverse events (AEs) were similar across the three study groups. The rates of arterial thromboembolic events (ATE) as defined by the Anti-Platelet Trialists' Collaboration (non-fatal stroke, non-fatal myocardial infarction, and vascular death) in the trial were 3% in the aflibercept group, 4% in the bevacizumab group, and 5% in the ranibizumab group (p =0.56). There were

more overall cardiovascular events in the ranibizumab group, compared to the aflibercept group and the bevacizumab group ($p < 0.01$); this included more cardiac events and cerebrovascular events in the ranibizumab group [32]. A recent Cochrane review did not find any difference between bevacizumab and ranibizumab in terms of all-cause death, all serious systemic adverse events, ATE, myocardial infarction, or stroke. There was a higher incidence of gastrointestinal disorders associated with bevacizumab treatment (relative risk 1.82) [33].

7. Switching Anti-VEGF Therapy for Refractory DME

For DME patients who do not respond well to repeated injections of intravitreal bevacizumab, the clinician has the option to try other anti-VEGFs, corticosteroids, or macular laser. Evaluation with OCT may help identify other causes of macular edema, such as vitreomacular traction, which may warrant surgical treatment. Fluorescein angiogram can also be used adjunctively to identify focal areas of leakage from microaneursyms, which may be amenable to laser treatment. As of now, no large randomized prospective clinical trials comparing treatment regimens for refractory DME have been published, but several smaller uncontrolled studies can provide some insight.

The REEF study (12 month prospective nonrandomized trial of 43 patients) found benefit in switching from bevacizumab to three monthly injections of 0.5 mg ranibizumab in patients with residual macular edema (CSFT >300 μm). Prior to the switch, patients had been treated with a mean of 4.7 bevacizumab injections with mean CSFT of 500 μm. Switching to ranibizumab resulted in additional reduction of 113 μm and 165 μm at 3 and 6 month follow up, respectively, with gains of 6.6 and 8.8 letters of

BCVA during the same time frames. Moreover, the 6/29 (20%) patients that did not respond adequately with ranibizumab 0.5 mg (CSFT reduction <10%) were switched to higher doses of three monthly 2.0 mg ranibizumab injections, which resulted in CSFT reduction >10% in 3 of 6 patients. Of note, the 2.0 mg dose of ranibizumab is not commercially available at this time [34].

Ciulla et al perfomed a retrospective review of 33 eyes with refractory DME that had been previously received an average of 5.1 treatments, including bevacizumab, triamcinolone, or macular laser. Switching to ranibizumab resulted in a statistically significant improvement in CSFT (from 384 μm to 335 μm), and BCVA (from 20/100 to 20/90) after an average of 7 injections over 48 week follow up. Statistical significance was achieved in relation to number of days follow up, but not for number of ranibizumab injections [35].

Lim et al performed a retrospective review of 21 eyes treated for DME that were unresponsive to either bevacizumab or ranibizumab (mean of 6 treatments), that were then converted to a median of 3 aflibercept injections and followed over a median of 5 months. CSFT improved significantly from 453 μm to 363 μm (-90 μm) after the first injection, and was 324 μm (-129 μm) at last follow up. BCVA improved significantly from logMAR 0.42 to 0.39 after one aflibercept, and then 0.37 logMAR at last follow up [36]. Wood et al reported that 11 of 14 (79%) eyes with persistent DME despite at least 3 injections of either bevacizumab or ranibizumab showed anatomic improvement after switching to aflibcercept; there was a 23% reduction of CSFT from 425 μm to 325 μm after 1 month ($p<0.0132$) [37]. Only 3 of 14 (21%) eyes had improved BCVA however.

8. Corticosteroids versus Anti-VEGF for DME

Chronic DME may differ even more in pathophysiology from non-chronic DME [38]. Anti-VEGF therapy may not be effective in all patients, because targeting VEGF does not suppress all the inflammatory cytokines and chemokines involved in DME. More recently, there has been interest in intravitreal corticosteroids, as the dexamethasone intravitreal implant (DEX) [39] and the fluocinolone acetonide implant (FA) [40, 41] have been approved for the treatment of DME in 2014. There are few large prospective clinical trials comparing anti-VEGF agents to corticosteroids as first line therapy in center-involved DME, but DEX and FA implants could become early treatment for pseudophakic patients particularly. DRCR protocol I compared 0.5 mg ranibizumab to 4 mg intravitreal triamcinolone acetonide; when analysis was confined to the pseudophakic group of patients to control for the effect of cataract formation, the group that received intravitreal triamcinolone acetonide plus prompt laser showed similar visual acuity results to the group that received ranibizumab plus prompt laser, as both groups gained a mean of 8 letters by 12 month follow up.[42].

In June 2014, the U.S. FDA approved a 0.7 mg dexamethasone implant (DEX) contained in a solid bioerodable polymer for the use in DME in pseudophakic patients or those phakic patients scheduled for cataract surgery. In September 2014, approval was expanded for the use in general DME patients, both pseudophakic and phakic, based on results of the MEAD study. After 3 years follow up, in which a mean of 4.1 DEX implants (0.7 mg) were administered, the DEX group experienced a mean CSFT reduction of 112 μm compared to 42 μm in the sham group. 22% of DEX 0.7 mg implant treated patients gained >15 letters BCVA compared to 12% in the sham group ($p<0.108$).

59% of the DEX 0.7 mg implant required cataract surgery compared to 7% in the sham group. 32% of the DEX group experienced IOP elevation ≥ 25 mmHg, 42% required IOP-lowering medications, and 0.6% required glaucoma incisional surgery [39].

The BEVORDEX study was a randomized prospective trial comparing bevacizumab every 4 weeks to DEX every 16 weeks in 88 eyes with center-involving eyes with DME. At 12 months, 40% of bevacizumab-treated patients gained 10 or more letters of BCVA, compared to 41% in eyes that received DEX, although 11% of DEX-treated eyes lost 10 or more letters of BCVA due to cataract formation. The DEX implant resulted in greater reduction of CSFT (-187 μm) than bevacizumab (-122 μm). The DEX group also received fewer injections (2.7) than the bevacizumab group (8.6) over the course of 12 months [43]. Maturi et al. compared efficacy of combination therapy with DEX and bevacizumab vs. continued bevacizumab monotherapy in 40 eyes that had refractory DME after multiple bevacizumab injections. The combination group received bevacizumab at baseline, and then DEX at months 1, 5, and 9. They also received bevacizumab as needed for CSFT >250 or ETDRS VA less than 80 letters. After 12 months, compared to continued monthly bevacizumab monotherapy, the combination group had greater reduction of CSFT (-45 μm vs -30 μm, p =0.03), though VA improvement was not statistically significant for the combination group (combined group: +5.4 letters, bevacizumab: +4.9 letters, p=0.75). The combined group needed 3 fewer bevacizumab injections, though this was counterbalanced by the need for a mean of 2.1 DEX injections [44].

A recent study compared the efficacy of fluocinolone acetonide (FA) sustained release implant in chronic (≥3 years duration) versus nonchronic (<3 years duration)

DME, as part of a preplanned subgroup analysis of the FAME trial. The non-erodable FA implant releases the drug for up to 36 months. At month 36, the difference between FA implant and sham control in the percentage of subjects who gained 15 letters or more was significantly greater in 536 chronic DME subjects (34.0% vs. sham, 13.4%; P<0.001), compared to the 416 subjects with nonchronic DME (22.3% vs. sham, 27.8%; P = 0.275). The differences could not be explained by baseline ocular characteristics, changes in anatomic features, or differences in re-treatment or ancillary therapies. The authors speculate that early DME is driven primarily by VEGF, while chronic DME may be driven more by inflammatory cytokines in addition to anatomic changes, and that intravitreal corticosteroids will inhibit the release of these inflammatory cytokines [38]. The results suggest that the FA implant may be an option for patients who do not respond to other therapy. This report may also partially account for the clinical observations of beneficial effect using the DEX implant when anti-VEGF agents have minimal effect.

Corticosteroid-related side effects were noted in the FAME study. Incisional glaucoma surgery was required by 4.8% of patients in the 0.2 μg/day (low dose FA) group and 8.1% of patients in the 0.5 μg/day (high dose FA) group. Cataracts progressed in nearly all phakic eyes. In September 2014, the FDA approved FA implant containing 0.19 mg fluocinolone for DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. However, this previous course of corticosteroids was not specified. Clinicians could conceivably trial a topical corticosteroid, intravitreal bolus therapy with triamcinolone, or DEX implant.

9. Conclusion

In summary, anti-VEGF therapy is the new treatment of choice for center-involved DME, as many studies have shown that it is superior compared to macular laser photocoagulation. Bevacizumab continues to be the most widely utilized anti-VEGF agent due to its cost-effectiveness. Recent data suggests that aflibercept is the most potent anti-VEGF treatment for DME, particularly in patients with ETDRS BCVA worse than 20/40 [32]. Smaller studies have demonstrated anatomic and functional benefit in switching to ranibizumab [34] or aflibercept [36] when initial treatment with bevacizumab fails. Ongoing studies are exploring the efficacy of combining anti-VEGF treatment with sustained-release corticosteroids to treat DME.

10. Expert Opinion

Despite growing clinical research data to support the use of anti-VEGF agents to treat DME, numerous questions remain. Most clinicians do not follow dosing regimens employed in registration trials, as many will follow an off-label "treat and extend" regimen, which has not been studied in large randomized clinical trials. Furthermore, it is unclear if there is as much a need to "treat until absolutely dry" as in exudative AMD. Many clinicians will switch between agents when there is suboptimal response; however, there is no consensus on the definition of suboptimal response or the definition of an appropriate trial of one agent before switching to another. One recent analysis of refractory DME cases from the VIVID/VISTA trials considered refractory DME to be <10% CSFT reduction after 12 weeks (Boyer DS, presented at Retina Society, Paris, France, October 8, 2015). We believe that a 12-week time frame and minimum of 3 anti-VEGF injections is a reasonable cutoff for defining refractory DME.

There are multiple controversial issues surrounding bevacizumab and other agents. Proponents of bevacizumab cite large cost disparities between bevacizumab ($50), ranibizumab 0.3 mg ($1170) and aflibercept ($1850), while others note that patient assistance programs are readily available to assist underinsured patients and potentially limit financial risk for physician practices. Furthermore, bevacizumab is used off-label, as it is repackaged and resold by compounding pharmacies, around which there have been some sterility issues, leading to increased regulation and more laborious patient-specific bevacizumab prescription requirements. More recently, there has been cost profiling by insurance companies, which has likely led to the controversial narrowing of panels and/or being dropped by insurance networks. Finally, retina specialists assume public relations risk in being identified as a large consumer of Medicare funds, due in part to the expense of the FDA-approved anti-VEGF agents.

The protocol-based ETDRS visual acuity used in DRCR Protocol T is often several lines better than the Snellen BCVA routinely obtained in the clinical setting, so the 20/50 cut off for treating with aflibercept may not directly translate to clinical practice. Adjusting for this, one may consider starting treatment with intravitreal bevacizumab for center-involved DME and only mild vision loss, especially when cost is an issue, as it has shown efficacy in reducing CSFT and improving BCVA. If CSFT or BCVA fails to improve after 2 bevacizumab injections, it may be prudent to switch to aflibercept or ranibizumab. One must also keep in mind that the strict monthly visits mandated in the clinical trials may not translate to clinical practice in the real world, where follow up may be less frequent and reliable, and with some patients being subsequently underdosed with anti-VEGF treatment.

While aflibercept was shown to be superior to ranibizumab in patients with ETDRS BCVA worse than 20/40 in DRCR Protocol T, these results may not apply to the population of refractory DME patients, whose pathophysiology could vary from those affected by treatment-naïve DME. As of now, one small retrospective series supports switching to aflibercept after patients have failed treatment with bevacizumab and ranibizumab, as it has been shown to result in statistically significant improvement in CSFT and BCVA [36]. Tachyphylaxis may partially explain the benefits achieved by switching from one anti-VEGF to another, as repeated doses of the same drug may result in diminishing effect. Larger prospective randomized clinical trials are needed to validate these findings. For those DME patients with ETDRS BCVA worse than 20/40, aflibercept is a first-line option, but its high cost continues to be a limiting factor for many patients despite the advantages of its 2-month injection frequency.

For non-centered involved refractory DME, laser treatment could remain an effective treatment, since the risks of laser photocoagulation are minimal in these cases, compared to the risks, discomfort, and expense of intravitreal therapies. After a series of anti-VEGF injections, a deferred focal laser therapy to localized areas of microaneurysm formation may decrease the number of required subsequent injections. For center-involved DME that is persistent despite periodic anti-VEGF therapy, the durable action of corticosteroid implants, such as the DEX and FA implants, facilitates combination therapy. The risks of sustained corticosteroid therapy, mainly glaucoma and cataract progression, should be carefully considered in the context of each patient. Pseudophakic patients, and those who have used a trial of corticosteroids without ocular hypertension, are preferred candidates for the DEX and FA implants.

Although the improvement in visual acuity and CSFT may seem modest after switching therapies, these cases of refractory DME can be especially difficult to treat, and consequently these modest improvements can be clinically meaningful, especially in patients with bilateral refractory DME. Bevacizumab, ranibizumab, and aflibercept each have different molecular sizes, binding affinities for VEGF, as well as different half-lives in the vitreous, and this could account for some of the differences noted between these agents. Aflibercept is the only available treatment that targets placental growth factor, which has an unclear role in the pathogenesis of DR, but animal studies suggest that it may contribute to blood-retinal barrier breakdown [45, 46].

Combining anti-VEGF treatment with sustained-release corticosteroids is a promising area of future research, as this approach may allow for more extensive control of the complex inflammatory pathways involved in DME. The synergistic effect of sustained-release corticosteroids may result in fewer anti-VEGF injections needed to keep DME under control. Currently, the DRCR Protocol U is exploring the efficacy of combination therapy with 0.3 mg ranibizumab and dexamethasone intravitreal implant compared to continued therapy with 0.3 mg ranibizumab to treat persistent DME. The results of DRCR Protocol T suggest the need for large prospective randomized trials to validate that switching from either bevacizumab to ranibizumab or aflibercept is superior to continued bevacizumab treatment in cases of persistent DME. Further study of refractory DME is warranted, given the visual disability caused.

Article Highlights Box

- The complex pathophysiology of DME involves upregulation of VEGF and other

inflammatory mediators.

- Anti-VEGF agents are first-line treatment for center-involved DME. Bevacizumab is a cost-effective and widely used anti-VEGF treatment, though aflibercept is the most effective option in patients with BCVA worse than 20/40 using ETDRS protocol eye charts.
- Some cases of DME are refractory to multiple bevacizumab treatments, and small studies report that switching to ranibizumab or aflibercept results in additional improvement in BCVA and macular thickness
- Future research will focus on efficacy of combined anti-VEGF and sustained-release corticosteroids to control refractory DME

Declaration of Interest:

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Bibliography

Papers of note have been highlighted as either of interest (*) or of considerable interest (**) to readers

1. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. Diabetes care 2003;26(9):2653-64.

2. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. Ophthalmology 1995;102(1):7-16.

3. Ferris FL, 3rd, Patz A. Macular edema. A complication of diabetic retinopathy. Surv Ophthalmol 1984;28 Suppl:452-61.

4. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol 1985;103(12):1796-806.

5. * Morello CM. Etiology and natural history of diabetic retinopathy: an overview. Am J Health Syst Pharm 2007;64:S3-7.

Excellent overview of the pathophysiology of DME.

6. Boyer DS, Hopkins JJ, Sorof J, et al. Anti-vascular endothelial growth factor therapy for diabetic macular edema. Ther Adv Endocrinol Metab 2013;4(6):151-69.

7. Diabetic Retinopathy Clinical Research N, Elman MJ, Aiello LP, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117(6):1064-77 e35.

8. Do DV, Nguyen QD, Khwaja AA, et al. Ranibizumab for edema of the macula in diabetes study: 3-year outcomes and the need for prolonged frequent treatment. JAMA Ophthalmol 2013;131(2):139-45.

9. Diabetic Retinopathy Clinical Research N, Elman MJ, Qin H, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. Ophthalmology 2012;119(11):2312-8.

10. Elman MJ, Ayala A, Bressler NM, et al. Intravitreal Ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. Ophthalmology 2015;122(2):375-81.

11. Nguyen QD, Shah SM, Khwaja AA, et al. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. Ophthalmology 2010;117(11):2146-51.

12. Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. Ophthalmology 2010;117(6):1078-86 e2.

13. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. Arch Ophthalmol 2012;130(8):972-9.

14. Ciulla TA, Harris A, Latkany P, et al. Ocular perfusion abnormalities in diabetes. Acta Ophthalmol Scand 2002;80(5):468-77.

15. Ehrlich R, Harris A, Ciulla TA, et al. Diabetic macular oedema: physical, physiological and molecular factors contribute to this pathological process. Acta Ophthalmol2010;88(3):279-91.

16. Miller JW, Le Couter J, Strauss EC, et al. Vascular endothelial growth factor a in intraocular vascular disease. Ophthalmology 2013;120(1):106-14.

17. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 2003;9(6):669-76.

18. Kim I, Moon SO, Kim SH, et al. Vascular endothelial growth factor expression of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin through nuclear factor-kappa B activation in endothelial cells. J Biol Chem 2001;276(10):7614-20.

19. Zhang X, Zeng H, Bao S, et al. Diabetic macular edema: new concepts in patho-physiology and treatment. Cell Biosci 2014;4:27

20. Noma H, Mimura T, Yasuda K, et al. Role of inflammation in diabetic macular edema. Ophthalmologica 2014; 232:127-135.

21. Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci USA 2002;99(17):11393-8.

22. Stefanini FR, Arevalo JF, Maia M. Bevacizumab for the management of diabetic macular edema. World J Diabetes 2013;4(2):19-26.

23. Arevalo, JF, Sanches JG, Wu L, et al. Primary intravitreal bevacizumab for diffuse diabetic macular edema: the Pan-American Collaborative Retina Study Group at 24 months. Ophthalmology 2009;116(8):488-97, 1497 e1.

24. Ferrara N, Damico L, Shams N, et al. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina 2006;26(8):859-70.

25. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology 2013;120(10):2013-22.

26. * Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012;119(4):789-801.

Landmark study that resuted in FDA approval of ranibizumab to treat DME

27. Bressler NM, Varma R, Suner IJ, et al. Vision-related function after ranibizumab treatment for diabetic macular edema: results from RIDE and RISE. Ophthalmology 2014;121(12):2461-72.

28. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011;118(4):615-25.

29. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. Ophthalmology 2015;122(10):2044-52.

30. ** Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. Ophthalmology 2014;121(11):2247-54.

Landmark study that resuted in FDA approval of aflibercept to treat DME

31. Stewart MW. The clinical utility of aflibercept for diabetic macular edema. Diabetes Metab Syndr Obes 2015;8:473-82.

32. ** Diabetic Retinopathy Clinical Research N, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015;372(13):1193-203.

The only large randomized clinical trial to directly compare bevacizumab, ranibizumab, and aflibercept in treating DME, which showed superiority of aflibercept in patients with BCVA worse than 20/40

33. Moja L, Lucenteforte E, Kwag KH, et al.,Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. Cochrane Database Syst Rev, 2014. 9: p. CD011230.

34. ** Dhoot DS, Pieramici DJ, Nasir M, et al. Residual edema evaluation with ranibizumab 0.5 mg and 2.0 mg formulations for diabetic macular edema (REEF study). Eye 2015;29(4):534-41.

Prospective study that reports efficacy of ranibizumab in treating DME refractory to bevacizumab treatment

35. Ciulla TA, Hussain RM, Ciulla LM et al. Ranibizumab for diabetic macular edema refractory to multiple prior treatments. Retina 2015 Nov 18 [Epub ahead of print]..

36. ** Lim LS, Ng WY, Mathur R, et al. Conversion to aflibercept for diabetic macular edema unresponsive to ranibizumab or bevacizumab. Clin Ophthalmol 2015;9:1715-8.

Retrospective review that reports improved BCVA and macular thickness for patients who switch to aflibercept after incomplete response with bevacizumab and ranibizumab

37. Wood EH, Karth PA, Moshfeghi DM, et al. Short-term outcomes of aflibercept therapy for diabetic macular edema in patients with incomplete response to ranibizumab and/or bevacizumab. Ophthalmic Surg Lasers Imaging Retina 2015. 46(9):950-4

38. Cunha-Vaz J, Ashton P, Iezzi R, et al. Sustained delivery fluocinolone acetonide vitreous implants: long-term benefit in patients with chronic diabetic macular edema. Ophthalmology 201;121(10):1892-903.

39. Boyer DS, Yoon YH, Belfort R, Jr., et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology 2014;121(10):1904-14.

40. Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology 2012;119(10):2125-32.

41. Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology 2012;119(10):2125-32.

42. Elman MJ, Bressler NM, Qin H, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2011;118(4):609-14.

43. Gillies MC, Lim LL, Campain A, et al. A randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular edema: the BEVORDEX study. Ophthalmology 2014;121(12):2473-81.

44. *Maturi RK, Bleau L, Saunders J, et al. A 12-Month, Single-Masked, Randomized Controlled Study of Eyes with Persistent Diabetic Macular Edema after Multiple Anti-Vegf Injections to Assess the Efficacy of the Dexamethasone-Delayed Delivery System as an Adjunct to Bevacizumab Compared with Continued Bevacizumab Monotherapy. Retina, 2015;35(8):1604-14.

Comparison of continued bevacizumab monotherapy vs. combination treatment with dexamethasone intravitreal implant and bevacizumab in cases of DME that did not show complete response to bevacizumab monotherapy

45. Kowalczuk L, Touchard E, Omri S, et al. Placental growth factor contributes to micro-vascular abnormalization and blood-retinal barrier breakdown in diabetic retinopathy. PloS One 2011;6(3):e17462.

46. Huang H, He J, Johnson D, et al. Deletion of placental growth factor prevents diabetic retinopathy and is associated with Akt activation and HIF1alpha-VEGF pathway inhibition. Diabetes 2015;64(1):200-12.

Table 1. Overview of select prospective randomized clinical trials regarding treatment of diabetic macular edema

Study Name	**Format**	**Anatomic Outcomes**	**BCVA Outcomes**
READ-2	0.5 mg IVR vs. laser only vs. combination (1:1:1)	*Mean CSFT at 24 months:* 0.5 mg IVR: 340 µm laser only: 286 µm combination: 258 µm	*Mean BCVA change at 24 months*: 0.5 mg IVR: +7.7 letters laser ony: +5.1 letters combination: +6.8 letters
RESTORE	0.5 mg IVR vs. laser only vs. combination (1:1:1)	*Mean CSFT change at 12 months:* 0.5 mg IVR: -119 µm laser ony: -61 µm combination: -128 µm	*Mean BCVA change at 12 months:* 0.5 mg IVR: +6.1 letters laser ony: +0.8 letters combination: +5.9 letters
RISE/RIDE	0.3 mg IVR vs. 0.5 mg IVR vs. sham (1:1:1)	*Mean CSFT change at 24 months (RISE/RIDE):* 0.3 mg IVR: -251/-260 µm 0.5 mg IVR: -253/-271 µm Sham: -133/-126 µm *Mean CSFT change at 36 months (RISE/RIDE):* 0.3 mg IVR: -261/ -262 µm 0.5 mg IVR: -269/ -267 µm Sham: -200/-213 µm	*Mean BCVA change at 24 months (RISE/RIDE):* 0.3 mg IVR: +12.5/+10.9 letters 0.5 mg IVR: +11.9/+12.0 letters Sham: +2.6/+2.3 letters *Mean BCVA change at 36 months (RISE/RIDE):* 0.3 mg IVR: +15.6/+12.8 letters 0.5 mg IVR: +12.0/+13.0 letters Sham: +7.6/+7.5 letters
DRCR.net Protocol I	Prompt laser only vs. 0.5 mg IVR + prompt laser vs. 0.5 mg IVR + deferred laser vs. 4 mg IVTA + prompt laser	*Mean CSFT change at 24 months:* 0.5 mg IVR + prompt laser: -144 µm 0.5 mg IVR + deferred laser: -170 µm 4mg IVTA + prompt laser: -95 µm Sham + prompt laser: -133 µm *Mean CSFT change at 60 months:* 0.5 mg IVR + prompt laser: -167 µm 0.5 mg IVR + deferred laser: -165 µm	*Mean BCVA change at 24 months:* 0.5 mg IVR + prompt laser: +7.0 letters 0.5 mg IVR + deferred laser: +10.0 letters 4mg IVTA + prompt laser: 0.0 letters Sham + prompt laser: +2.0 letters *Mean BCVA change at 60 months:* 0.5 mg IVR + prompt laser: +7.2 letters 0.5 mg IVR + deferred laser: +9.8 letters
BOLT	1.25 mg IVB vs. laser only (1:1)	*Mean CSFT change at 12 months*: 1.25 mg IVB: -129 µm laser only: -68 µm *Mean CSFT change at 24 months:* 1.25 mg IVB: -146 µm	*Median BCVA change at 12 months:* 1.25 mg IVB: +8.0 letters laser only: -0.5 letters *Mean BCVA change at 24 months:* 1.25 mg IVB: +8.6 letters

		laser only: -118 µm	laser only: -0.5 letters
VIVID & VISTA	IVA 2q4 vs. IVA 2q8 (after 5 monthly doses) vs. laser	*Mean CSFT change at 12 months (VISTA/VIVID):* IVA 2q4: -186/-195 µm IVA 2q8: -183/-192 µm laser: -73/-66 µm *Mean CSFT change at 100 weeks:* IVA 2q4: -191.4/-211.8 µm IVA 2q8: -191.1/-195.8 µm laser: -83.9/-85.7 µm	*Mean BCVA change at 12 months (VISTA/VIVID):* IVA 2q4: +12.5/+10.5 letters IVA 2q8: +10.7/+10.7 letters laser: +0.2/+1.2 letters *Mean BCVA change at 100 weeks:* IVA 2q4: +11.4/+11.5 letters IVA 2q8: +9.4/+11.1 letters laser: +0.7/+0.9 letters
DRCR.net Protocol T	IVA 2 mg vs. IVR 0.3 mg vs IVB 1.25 mg (1:1:1)	*Mean CSFT change at 12 months:* IVA 2 mg: -169 µm IVR 0.3 mg: -147 µm IVB 1.25 mg: -101 µm	*Mean BCVA change at 12 months:* IVA 2q4: +13.3 letters IVR 0.3 mg: +9.7 letters IVB 1.25 mg: +11.2 letters
MEAD	DEX 0.35 mg vs. DEX 0.7 mg vs. sham (1:1:1)	*Mean CSFT change at 36 months*: Dex 0.35 mg:-108 µm Dex 0.7 mg: -112 µm sham: -42 µm	*Mean BCVA change at 36 months:* Dex 0.35 mg: +3.6 letters Dex 0.7 mg: +3.5 letters sham: +2.0 letters
FAME	FA 0.2 µg/day vs. FA 0.5 µg/day vs. sham (2:2:1)	*Mean CSFT change at 24 months:* FA 0.2 µg/day: -177 µm FA 0.5 µg/day: -168 µm sham: -111µm	*Mean BCVA change at 24 months:* FA 0.2 µg/day: +4.4 letters FA 0.5 µg/day: +5.4 letters sham: +1.7 letters

READ, Ranibizumab for Edema of the Macula in Diabetes; IVR, intravitreal ranibizumab; CSFT, central subfield thickness; BCVA, best corrected visual acuity; RESTORE, Efficacy and Safety of Ranibizumab in Patients With Visual Impairment Due to Diabetic Macular Edema; RISE/RIDE, Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus; DRCR, Diabetic Retinopathy Clinical Research Network; IVTA, intravitreal triamcinolone acetonide; BOLT, Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema; IVB, intravitreal bevacizumab; VIVID/VISTA, Intravitreal Aflibercept Injection in Vision Impairment due to DME; FAME, Fluocinolone Acetonide for Diabetic Macular Edema; FA, fluocinolone acetonide

Table 2

Inflammatory markers upregulated in DME
Vascular Endothelial Growth Factor
Interleukin-6
Tumor necrosis factor-alpha
Monocyte chemotactic protein-1
Cyclooxygenase-2
Pentraxin3
Interleukin-8
Intercellular Adhesion Molecule-1