

Treatment of Diabetic Macular Oedema – Clinical Trial Findings and Real-world Outcomes Data

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Abstract

In recent years, several intravitreal drug applications have become available for the treatment of diabetic macular oedema (DME). This review aims to summarise and compare available results. Based on a PubMed search, appropriate studies or reviews were evaluated. Clinical trial data suggest that the intravitreal administration of both vascular endothelial growth factor (VEGF) inhibitors and corticosteroids is effective and that overall outcomes are comparable between treatments. Sustained delivery of corticosteroids presents a less treatment-intensive alternative, potentially reducing side effects and enhancing compliance. Compared with clinical development data, recent findings from clinical practice suggest a lesser, more flexible injection frequency in VEGF inhibitors is associated with less pronounced efficacy results. In contrast, corticosteroids treatment frequency seems to correspond with pivotal trial results, reporting equal (or slightly higher or lower) treatment schedules, resulting in similar or higher efficacy values. Safety issues differ between drug classes. Corticosteroid side effects are essentially of local nature and mainly consist of intraocular pressure increases and progression of cataract, limiting their use to pseudophakic patients or those for whom alternative treatments are not effective or are inappropriate. Anti-VEGF treatment is also associated with ocular side effects, but also with reports on systemic side effects, such as myocardial infarctions or vascular thromboembolic events. More long-term clinical practice data need to be generated to inform about effectiveness and safety of available therapies in specific patient populations.

Keywords

Aflibercept, bevacizumab, biodegradable, corticosteroids, dexamethasone, diabetic macular oedema, fluocinolone, intravitreal, non-biodegradable, ranibizumab, sustained drug-delivery systems, vascular endothelial growth factor (VEGF) inhibitors

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Diabetic macular oedema (DME) is a severe ocular complication of diabetic retinopathy (DR).¹ Despite the fact that significant advances are being made in early diagnosis and treatment of patients, numbers of patients likely to develop vision loss or blindness due to DR and DME are expected to rise in parallel to the incidence of diabetes. Estimates have projected that, by 2050, there will be in excess of 50 million diabetics in the US, half of whom are projected to develop diabetic retinopathy.²⁻⁴

The treatment of DME has evolved dramatically over the past decade. While laser therapy presented the standard of care for many years,⁵ recent times have seen the introduction of several new therapeutic approaches. All of these therapies have in common that they are applied intravitreally. For many of these treatments, initial data from pivotal clinical trial programmes are now being supplemented by clinical practice data. This article aims to identify and review the available data to determine how newer therapies perform in real-world practice compared with the initial clinical trial setting.

A search of the US National Library of Medicine, National Institutes of Health (<http://www.ncbi.nlm.nih.gov/pubmed>) was performed

for the time period between June 2009 and March 2016, based on the following search terms: “diabetic macular edema” and “outcomes” and the respective active compound (“aflibercept”, “bevacizumab”, “dexamethasone”, “fluocinolone” or “ranibizumab”). Publications of individual study reports as well as review articles were included to generate a balanced review of the current state of play.

The two fundamental therapeutic groups now available for the indication of DME are VEGF inhibitors and corticosteroids.

Intravitreal anti-vascular endothelial growth factor therapies

Licensed vascular endothelial growth factor (VEGF) inhibitors include ranibizumab and aflibercept. Additionally, bevacizumab is used as an off-label option in clinical practice.

Ranibizumab and bevacizumab

Key information on study set up as well as study results for ranibizumab and bevacizumab are listed in *Table 1*.

Table 1: Anti-VEGF compounds - summary of results from clinical trials

Trial	Interventions	Efficacy Outcomes VA (CRT)	Safety
Brown et al 2013 (RISE) Prospective	Ran 0.5 mg, (Ran 0.3 mg) vs. sham/Ran 0.5mg in 377 patients	BCVA gain of more than 15 letters after 36 months: 41.6% vs 22% (p=0.0002) Mean BCVA gain of 11 (SD 12.9) letters in Ran 0.5 mg vs. sham 4.3 (SD 14.9) Reduction in CFT: 269.1 µm vs 200.1 µm	IOP increase Ran 0.5 mg vs. sham: 14% vs. 2% APTC events RISE AND RIDE: Ran 0.5 mg: 10.4%; Sham/Ran 0.5 mg 7.2%
Brown et al 2013 (RIDE) Prospective	Ran 0.5 mg, (Ran 0.3 mg) vs. sham/Ran 0.5 mg in 382 patients	BCVA gain of more than 15 letters after 36 months: 40.2% vs 19.2% Mean BCVA gain of 11.4(SD16.3) letters in Ran 0.5 mg vs. sham 4.7 (SD 13.3) Reduction in CFT: 261 µm vs 213 µm Delayed treatment in patients receiving sham did not lead to same extent of vision gain	IOP increase Ran 0.5 mg vs. sham: 18.5% vs. 11% APTC events RISE and RISE: see above
Massin et al. 2010 (RESOLVE) Prospective	Ran 0.5 mg, (Ran 0.3 mg) vs. sham in 382 patients in 151 patients	BCVA (EDTRS) gain at 12 months: 8.8 letters (p<0.001 vs. sham) vs. 11.8 vs. -1.4 letters	IOP increase Ran 0.5 mg vs. sham: 29% vs. 2%
Mitchell et al. 2011 (RESTORE) Prospective	Ran 0.5 mg vs Ran 0.5 mg plus laser vs. laser in 345 patients	BCVA (EDTRS) gain at 12 months: 6.1 letters (p<0.001 vs. laser) vs. 5.9 (p<0.001 vs. laser) vs 0.8 letters CRT reduction 128 vs 119 vs 61 µm	IOP increase Ran 0.5 mg vs. Ran 0.5 mg plus laser: <1% vs. <1% Arterial thrombo-embolic events (ATE) 5% vs. <1%
Schmidt-Erfurth et al. 2014 (RESTORE extension study)	Individualized Ran 0.5 mg in 208 patients	BCVA (EDTRS) gain from baseline at month 36: Prior Ran 0.5 group: 8 letters Prior Ran 0.5 mg plus laser: 6.7 letters Prior laser only: 6 letters Mean number of injections: 6.5 from months 12–36 CRT reduction: Prior Ran 0.5 group: 142.1 µm Prior Ran 0.5 mg plus laser: 145.9 µm Prior laser only: 142.7 µm	Cataract incidence: 16.3%
Ohji et al. 2012 (REVEAL) Prospective	Ran 0.5 mg vs Ran 0.5 mg plus laser vs. laser in 396 patients	BCVA (EDTRS) at 12 months: 5.9 letters (p<0.001) vs. 5.7 (p<0.001) vs 1.4 letters	
Googe J et al. 2011 DRCR.net	Sham vs Ran 0.5 mg vs Triamcinolone 4 mg Focal/grid laser for DME Prompt PRP for DR in 145 eyes	Mean change in BCVA from baseline at 14 weeks: Sham group: -4±14 Ran 0.5 group: 1±11 (p<0.001) Triam 4 mg group: 2±11 (p<0.001)	56 weeks safety outcomes: cerebrovascular/cardiovascular events: Sham: 4% Ran 0.5 mg: 7% Triamcinolone: 3%
Elman et al. 2015 DRCR.net Prospective	Ran 0.5 mg plus prompt laser vs. Ran 0.5 mg plus deferred laser in (163 + 150) patients for ≤ 24 weeks in DME involving central macula	The mean change in VA from baseline through the 5-year visit: 7.2 letters vs.9.8 letters (p=0.09) Improvement of ≥10 letters in 46% vs. 58%, Improvement of >15 letters in 27% vs. 38%	
Bressler et al. 2016 DRCR.net (Protocol I) Prospective	Ran 0.5 mg plus deferred laser vs. Ran 0.5 mg plus prompt laser vs laser/very deferred Ran 0.5 mg vs triamcinolone plus laser/very deferred Ran 0.5 mg at total of 828 eyes	Mean change at 5 years in VA (±SD): RL(D): 10±13.8 RL(P): 10±13.5 L(DR): 5±14 TL(DR): 7±14	
Menchini et al. 2015 (PRIDE)	Ran 0.5 mg, laser as needed in 515 patients (unilateral and bilateral treatment); 10% naïve patients	Mean VA gain in decimal scores (±SD) at month 5: Unilateral: 1.5 ± 2.38 Bilateral: 1.22 ± 1.67	Eye disorders: 3.18%/4.18% respectively Cardiac disorders:1.27%/1.23% Vascular disorders: 0.64%/0.66%
Wells et al. 2016 DRCR.net (Protocol T)	Ran 0.3 mg, Bev 1.25 mg or AFL 2.0 mg Laser as needed in 660 patients with VA 20/50 to 20/320 or VA 20/32 to 20/40	Mean VA gain at 2 years: Ran 12.3, Bev 10.0, AFL12.8 VA gains in patients with VA 20/32 to 20/40: Ran 8.6, Bev 6.8, Afl 7.8	Anti-Platelet Trialists' Collaboration (APTC) events: Ran 12%, Bev 8%, AFL 5%
Michaelidis et al. 2010 (BOLT)	Bev 1.25 mg vs laser in 80 patients	Mean gain in BCVA at 24 months: Bev: 8.6 letters Laser: -0.5 letters Patients gaining BCVA of ≥ 10 EDTRS letters at 24 month: Bev: 49% (p<0.001 vs laser), laser: 7%	No significant ocular events No systemic AEs

Table 1: Cont.

Trial	Interventions	Efficacy Outcomes VA (CRT)	Safety
Lam et al. 2009	Bev 1.25 mg vs. Bev 2.5 mg in 52 patients	Mean BCVA gain in EDTRS letters at month 6: Bev 1.25: 5.5 letters Bev 2.5: 6.5 letters	No significant ocular events, no systemic events
Do et al.2012 (DA VINCI)	AFL 0.5q4, AFL 2q4 vs. AFL 2q8 vs AFL PRN, laser in 221 patients	Mean change in BCVA (EDTRS letters) at week 52: 11.0 vs 13.1 vs 9.7 vs 12.0 vs -1.3% of eyes with a BCVA gains of >15 letters: 40.9 vs 45.5 vs 23.8 vs 42.2 vs 11.4 Mean reduction in CRT (μm): -165.4 vs 227.4 vs 187.7 vs 180.3 vs -58.4	Increased IOP in 11% of patients only 2 patients had an increase of >10 mmHg
Brown et al. 2016 VIVID	AFL 2q4 vs. AFL 2q8 vs laser in 406 patients	Mean change in BCVA (EDTRS letters) at month 12: 10.5 vs. 10.7 vs 1.2 Mean BCVA gain at 100 weeks: 11.4, 9.4 and 0.7 letters ($p<0.0001$) Proportion of eyes with >15 letter gain at week 100: 38.2, 31.1 and 12.1% ($p<0.0001$)	Most frequent serious ocular adverse event was cataract (2.4%, 1.0% and 0.3% for 2q4, 2q8 and laser)
Brown et al.2016 VISTA	AFL 2q4 vs. AFL 2q8 vs laser in 466 patients	Mean change in BCVA (EDTRS letters) at month 12: 12.5 vs. 10.7 vs 0.2 Mean BCVA gain at 100 weeks: 11.5, 11.1 and 0.9 letters ($p<0.0001$) Proportion of eyes with >15 letter gain at week 100: 38.3, 33.1 and 13.0% ($p<0.0001$)	Most frequent serious ocular adverse event was cataract (2.4%, 1.0% and 0.3% for 2q4, 2q8 and laser)
Rahimy et al. 2016	AFL in 50 eyes previously treated with Ran or Bev	Mean change of VA (logMAR): -0.05 ± 0.22 ($p=0.12$) Mean decrease in CMT of $112 \pm 141 \mu\text{m}$ ($p<0.0001$)	

Ranibizumab was initially investigated in DME patients in a phase I/II open-label evaluation (READ-2 study) as well as a phase II trial (RESOLVE).⁶ Several phase III studies in DME followed. The RISE and RIDE studies were two parallel studies which ran for a time period of 36 months. Gains in visual acuity (VA) and improvement in retinal anatomy was sustained over three years. The proportions of patients who gained at least 15 letters from baseline in the sham/0.5 mg, 0.3 mg and 0.5 mg ranibizumab groups were 19.2%, 36.8% and 40.2%, respectively, in RIDE and 22.0%, 51.2% and 41.6%, respectively, in RISE.⁷

REVEAL and RESTORE compared ranibizumab alone to laser alone or to combination treatment. Notably, the addition of laser did not confer additional benefit.⁸ The RESTORE three-year outcomes study demonstrated that ranibizumab was effective in improving and maintaining best corrected visual acuity (BCVA), central retinal thickness (CRT) outcomes with a progressively declining number of injections per year (mean of <3 injections).⁹

Real-world clinical practice data are also available from open-label extensions of the original clinical trials, as well as from post-licensing studies, giving physicians the opportunity to inject the product on an as-needed basis (PRN, pro re nata). Data from the extension of RESTORE demonstrated that improvements in BCVA and CRT were also maintained at year three, with patients requiring fewer injections over this time.⁷

The Diabetic Retinopathy Clinical Research Network (DRCR.net) study demonstrated that the addition of one intravitreal triamcinolone or two ranibizumab injections in eyes receiving focal/grid laser for DME and panretinal photocoagulation (PRP) is associated with better visual acuity and decreased macular oedema by 14 weeks.¹⁰ Another DRCR.net study, performed in patients with decreased VA and DME

involving the fovea over five years, reported that patients treated with ranibizumab plus prompt laser or ranibizumab plus deferred laser maintained visual gains from year 1 to 5, requiring less treatment after year 3. Notably, patients from the latter group required more ranibizumab injections.¹¹ A similar study included two additional patient groups receiving laser-only or triamcinolone plus deferred ranibizumab. Authors concluded that eyes receiving initial ranibizumab treatment are likely to have better long-term vision improvements.¹² An Italian study provided additional evidence. Use of ranibizumab was well tolerated and improved or maintained VA in 40.2% to 68.8% of patients, with no difference between unilateral or bilateral cases.¹³

A recent DRCR.net study compared the effectiveness of aflibercept, ranibizumab or bevacizumab for DME over two years (PROTOCOL T). The median number of injections was 15, 16 and 15, respectively over two years, with lesser injections in year 2. Overall, all three treatments improved VA from baseline. While VA outcomes were similar for eyes with better baseline VA, aflibercept had better outcomes compared with bevacizumab over two years, as well as to ranibizumab over the first year in eyes with worse baseline VA. Higher Anti-Platelet Trialists' Collaboration (APTIC) event rates with ranibizumab warrant a continued evaluation in future trials.¹⁴

Bevacizumab is not licensed for the indication of DME, however, it is used in current medical practice. Several studies have demonstrated the efficacy and safety of bevacizumab in DME. The BOLT study compared use of bevacizumab with laser treatment (see *Table 1*).¹⁵ Faghihi et al. reported a similar injection rate and efficacy for bevacizumab 1.25 mg and bevacizumab 1.25 mg plus a single laser treatment over a period of six months.¹⁶ In a six-month study in patients with diffuse DME, Lam et al. demonstrated a similar efficacy of two different doses of bevacizumab (1.25 mg and 2.5 mg).¹⁷ Additional trials have investigated

a combination of bevacizumab 1.25 mg and triamcinolone 2 mg. Ahmadiet al. found that the BCVA for the combination was not significantly better than bevacizumab alone.¹⁸ Soheiliet al. compared bevacizumab 1.25 mg plus triamcinolone 2 mg versus bevacizumab alone and laser alone. Results at 24 months did not favour any of the groups. Lim et al. demonstrated that treatment with a combination of bevacizumab plus triamcinolone, bevacizumab alone or triamcinolone alone did not yield statistically differences between groups in terms of BCVA and CMT. The ATEM study also found comparable efficacy in the bevacizumab 1.25 mg plus triamcinolone 4 mg group and each monotherapy alone. The adverse event profile is comparable to ranibizumab. Studies are not powered to detect small differences in rates of infrequent events. Overall, bevacizumab was well tolerated.⁸

Aflibercept

Key information on study set up as well as study results for aflibercept are listed in *Table 1*.

A multicentre phase II study evaluated the efficacy and safety of different aflibercept concentrations compared with laser in DME patients. Significant gains in BCVA from baseline achieved at week 24 were maintained or improved at week 52 in all aflibercept groups.¹⁹

The efficacy and safety of aflibercept 2 mg applied monthly (2q4) or every two months (2q8) was compared with laser treatment in two phase III studies. The authors concluded that, in both studies (VISTA and VIVID), the 52-week anatomical and visual superiority of aflibercept injections over laser treatment were significant and similar at week 52 and through week 100. At week 100, the mean BCVA gain was 11.4, 9.4 and 0.7 letters in VIVID and 11.5, 11.1 and 0.9 letters in VISTA for aflibercept 2q4, aflibercept 2q8 and laser, respectively.²⁰ Real-world outcomes in 50 eyes with persistent DME previously treated with ranibizumab or bevacizumab and then switched to aflibercept were recently reported by Rahimy and colleagues. Conversion to aflibercept resulted in significant anatomic improvements, but only trends towards improved visual acuity and reduction in IOP were observed.²¹

Intravitreal corticosteroid delivery systems Fluocinolone

Key information on study set up as well as study results for fluocinolone are listed in *Table 2*.

The long-term efficacy and safety of the FAC non-degradable implant was assessed in patients with persistent DME in spite of one or more laser treatments. Subjects were eligible for laser rescue treatment six weeks after injection. Almost all phakic patients in the FAC implant groups developed cataract. However, their actual visual benefit, as determined after removal of the cataract, was similar to pseudophakic patients in the study. IOP elevations considered an adverse event (AE) were reported in approximately 35% of patients receiving FAC 0.2µg/day.²² In the active group, 18.7% of patients received two and 6.3% three or more implants. Laser treatment was administered in 40% of patients in the active group. Also 13.4% of patients from this group received additional off protocol treatments such as intravitreal triamcinolone or anti-VEGF compounds. It was concluded that the FAC 0.2 µg/d implant provided substantial benefit for up to three years and thus would provide an option for patients who do not respond to other therapies.²³ A recent study produced data in six pseudophakic patients with bilateral, chronic DME previously treated with laser and anti-VEGF therapy. The FAC implant in both eyes was a feasible, effective second-

or third-line choice for patients with severe bilateral DME, without notable increases in IOP.²⁴

Dexamethasone

Key information on study set up as well as study results for dexamethasone are listed in *Table 2*. The DEX implant contains 700 µg dexamethasone in an inactive biodegradable polymer matrix. The latter ultimately degrades to water and carbon dioxide and dexamethasone is released over six months. It is indicated patients who have not respond sufficiently to non-corticosteroid treatment, pseudophakic patients and patients deemed to be unsuitable for non-corticosteroid treatment. Efficacy and safety of dexamethasone biodegradable implant is reported in several phase II and III trials. PLACID was a 52-week, masked, multicentre, randomised, sham-controlled phase II trial.²⁵ CHAMPLAIN was a 26-week, open-label trial to assess the safety and efficacy of DEX implant in patients with DME who had had pars plana vitrectomy. Patients with DME and a history of vitrectomy showed a benefit of treatment up to six months after implantation in terms of reduction of macular thickness and increase in BCVA.²⁶

The MEAD study, a phase three trial, included a total of 1,048 patients. After the first DEX implant treatment, an additional implant could be administered every six months if the thickness of the oedema increased or persistent oedema was present. Patients could receive up to seven treatments during the trial. A very rapid initial response was demonstrated in BCVA values, maintaining statistical significance up to approximately 15 months. This was followed by a drop in BCVA, coinciding with the development of cataract. A subgroup analysis of the patients that were pseudophakic at baseline (approx. 25%) showed consistency in BCVA improvement throughout the three-year study period compared to sham. Visual acuity decreased between the time of reporting cataract adverse event and cataract surgery but improved to pre-cataract levels after surgery.²⁷ A subgroup analysis of patients previously treated for DME (with laser, anti-VEGF therapies, IVTA or a combination of these therapies) showed that the DEX implant significantly improved visual and anatomic outcomes.²⁸ The BEVORDEX trial compared efficacy and safety of the DEX implant with bevacizumab. At month 12 the percentage of patients reported with ≥ 10 logMAR letters were 40 in the DEX implant and 41 in the bevacizumab group, while CMT was reduced by 187 µm and 122 µm, respectively.²⁹ The VA improvement in both groups was maintained at 24 months, while the CMT reduction in the bevacizumab group caught up to be comparable with the DEX implant group. The injection frequency difference for both groups was less pronounced in year 2, still favouring the DEX implant.³⁰ A 12-month single-masked, randomised controlled study comparing the efficacy of bevacizumab 1.25 mg with a combination of bevacizumab 1.25 mg and the DEX implant in eyes with persistent ME came to the conclusion that the combination significantly improves visual acuity as well as the morphology of refractory DME, although VA gains were not superior to continued bevacizumab therapy.³¹

Recently, data from use of the DEX implant in clinical practice has also become available. A prospective study compared the efficacy of a single administration of DEX implant with monthly intravitreal injections of ranibizumab. After three months, DEX implant showed a better efficacy (mean VA gain of 8.5 vs. 4 letters). This significance was lost after six months (overall VA gain of 2.5 vs. 2 letters).³² A prospective study comparing bevacizumab administered as monotherapy with the DEX implant in the treatment of persistent DME reported that both groups had similar VA gains, while patients in the DEX implant group

Table 2: Corticosteroids - Summary of results from clinical trials and real world data

Trial	Interventions	Primary Efficacy Outcome	Safety
Campochiaro et al. 2012 (FAME)	FAC implant 0.2µg/day (375 patients), FAC implant 0.5µg/day (393 patients), sham (185 patients); mean duration DME in years: FAC 0.5µg: 3.5 (±2.6), sham: 3.9 (±3.78)	BCVA % patients ≥ 15 EDTRS letters at month 36: FAC 0.2µg: 28.7, (FAC 0.5µg:27.8),Sham: 18.9 (p= 0.018) Mean change letters from baseline BCVA at month 36: active: 7.6; sham:1.8	Cataract surgery rate FAC 0.2µg: 80% Glaucoma surgery rate FAC 0.2µg: 4.8%
Cunha-Vaz et al. 2014 (FAME)	FAC implant 0.2µg/day (209 patients), sham (112 patients) Subgroups chronic patients (>3 years)	BCVA % chronic patients ≥ 15 EDTRS letters at month 36: FAC 0.2µg: 34, Sham: 13.4 (p<0.001)	Cataract surgery rate: FAC: 85.1% Glaucoma surgery rate: FAC: 5.3%
Yang et al 2015 (FAME)	FAC implant 0.2µg/day Subgroup: phakic (188 patients) versus pseudophakic (140 patients); median duration DME: 1.73 years	BCVA % patients ≥ 15 EDTRS letters at month 36: Phakic: 29.3 Pseudophakic: 35.1	
Elaroud et al 2016	FAC 0.2µg/day (6 pseudophakic patients with chronic DME)	Mean change in BCVA 10 letters (±12.2 letters)at 6 months	Mean IOP was 16.1 mmHg; mean change of 1.1mmHg (SD±3.6)
Callanan et al. 2013 (PLACID)	DEX implant 0.7 mg plus laser (126 patients), laser (127 patients) in diffuse DME	Maximum mean VA increase in letters from month 1 to 9: Dex/laser: 7.7; laser: 2.8 Primary efficacy endpoint of demonstrating benefit of combination over laser at month 12 in terms of proportion of patients gaining ≥ 10 letters was not met	DEX/Laser: IOP elevation in 20% of patients; IOP rise of ≥10 mmHg: 1% patients Laser: IOP rise of ≥10 mmHg: 0% patients Cataracts: not reported
Boyer et al. 2011 (CHAMPLAIN)	Open-label efficacy and safety of Dex 0.7 mg in patients with pars plana vitrectomy	Change from baseline at 26 weeks : reduction of CMT, Increase of VA	17% of patients started taking IOP-lowering medication during study period No patient required laser or surgical procedure to control IOP, discontinued study because of elevated IOP
Boyer et al. 2014 (MEAD)	DEX implant 0.7 mg (351 patients), DEX implant 0.35 mg (347 patients), sham (350 patients) Prior treatments in %: laser (67); intravitreal steroids (18), anti-VEGF (9) Mean DME duration: 24 mos	BCVA % patients ≥ 15 EDTRS letters at month 36: DEX 0.7 mg: 22; Sham: 12 (p<0.018) Mean average reduction over 36 months versus baseline: DEX 0.7 mg: -111.6 µm; Sham: -41.9 µm (p< 0.001). Similar effect of DEX 0.7 mg in subgroups defined by DME duration	Cataract surgery rate DEX: 59%,Sham: 7.2% Increased IOP: DEX: 36%, Sham 5% IOP lowering medication in DEX: 42% Glaucoma surgery rate: DEX: 0.6%, Sham 0%
Augustin et al. 2015 (MEAD)	DEX implant 0.7 mg (247 patients), sham (261 patients) Subgroup: previously treated patients Mean DME duration in mos: DEX 0.7 mg: 27.3 (±26.3); sham: 31.9 (±28.6)	BCVA % patients ≥ 15 EDTRS letters at month 36: DEX 0.7 mg: 21.5 Sham: 11.1 (p=0.002)	Cataract related events DEX: 70.3%, Sham: 20.1% IOP related events: DEX: 38.1%, Sham: 4.6%
Gillies et al 2014 (BEVORDEX)	DEX implant 0.7 mg (46 eyes), Bevacizumab 1.25 mg (42 eyes)	BCVA % patients ≥ 10 logMAR letters at month 12: DEX 0.7 mg: 40 Becavizumab 41 (p=0.83) Reduction in central retinal thickness Dex: -187µm; Bev: -122µm (p=0.015). Mean injections to month: DEX 0.7 mg: 2.8 (SD 0.9) Becavizumab:9.1 (SD 3.1)	
Fraser-Bell et al. 2016	DEX implant 0.7 mg (46 eyes), Bevacizumab 1.25 mg (42 eyes)	BCVA % patients ≥ 10 logMAR letters at month 24: DEX 0.7 mg: 43 Becavizumab 45 (p=0.99) Mean injections from month 12-24: DEX 0.7 mg: 2.2 (SD 1.2) Becavizumab:4.8 (SD 5.1)	
Pacella et al. 2014 Prospective	DEX implant 0.7 mg (25 eyes) Becavizumab 1.25 mg (25 eyes); DME duration in mos: 46.3 (±18.6)	Mean VA gain after 3 months: 8.5 letters vs. 4 letters	

Table 2: Cont.

Trial	Interventions	Primary Efficacy Outcome	Safety
Maturi et al. 2015 Prospective	DEX implant 0.7 mg plus bevacizumab 1.25 mg versus bevacizumab 1.25 mg alone in 40 eyes	Mean VA gain from baseline at month 12 : Combination group: +5.4 letters Bevacizumab group: 4.9 letters (p= 0.75) Mean reduction in CMT: Combination group: 45 µm Bevacizumab group: 30 µm (p=0.03)	
Shah et al. 2016 Prospective	DEX implant 0.7 mg versus bevacizumab 1.25 mg In 50 eyes	Mean change in BCVA at month 7: Bevacizumab 1.25 mg: +5.6±6.1 letters DEX implant: +5.8 ±7.6 letters (p=0.785) Mean change in CST: Bevacizumab 1.25 mg: -13± 105 µm DEX implant: -122 ± 120 µm Number of injections: Bevacizumab 1.25 mg: 7 ± 0.2 DEX implant: 2.7 ± 0.5	
Guigou et al. 2015 Retrospective	DEX implant 0.7 mg (74 patients) Follow up over a mean of 9.8 months	Mean VA gain of 8.5 letters and 7.6 letters after 2 and 6 months respectively Patients with a gain of ≥ 15 letters at month 6: 27% Patients with a normal CRT at month 6: 34.4%	Ocular hypertension ≥25 mmHg seen in 13.4% patients at month 2; IOP controlled by topical treatment At 6 months, hypertension was only observed in 2% patients
Escobar-Barranco et al. 2015 Prospective	DEX implant 0.7 mg (40 refractory and 30 naïve patients) Laser use as needed	VA mean gain in EDTRS letter improved significantly in both groups (p<0.001). Naïve gained significantly more compared to refractory patients (p<0.001) e.g mean increase of 14 vs 8 letters at month 2	Transient IOP increase: 7.9% Cataract: 2.6% Retinal haemorrhage: 2.6% Vitreous haemorrhage: 3.9% No endophthalmitis or retinal detachment
Dutra Medeiros et al. 2014 Retrospective	DEX implant 0.7 mg (58 refractory patients after laser or anti-VEGF treatment) Refractory: edema of more than 250µm lasting at least 90 days after laser or anti VEGF treatment	VA peak gain of 0.22 logMAR (Logarithm of the Minimum Angle of Resolution) and CRT reduction of 202 µm after 3 months	
Totan et al. 2015 Prospective	DEX implant 0.7 mg (30 refractory eyes, previously treated with bevacizumab monthly for 3 months DME duration ≥ 6 months	Mean BCVA increase from 0.56 to 0.41(p<0.001) and 0.44 (p=0.008) at month 1 and 3 respectively Mean CFT significantly decreased from 517µm at baseline to 290µm (p<0.001), 314µm (p<0.001) and 411µm (p=0.01), at months 1, 3, and 6 respectively.	Significant IOP increase at week 1 (p<0.01), month 1 (p<0.01) and month 3 (p=0.04). Eyes with IOP>21mmHg were well controlled on topical therapy
Lazic et al. 2014 Prospective	DEX implant 0.7 mg (15 refractory patients, previously treated unsuccessfully with bevacizumab)	Mean BCVA increase after 2 months from 0.29 to 0.39 Snellen lines (p=0.0038) Mean CFT decreased from 462 µm to 346 µm (p=0.0288).	
Medeiros et al. 2014 Retrospective	DEX implant 0.7 mg (54 refractory patients; vitrectomized and non vitrectomized eyes)	At month 6: Similar findings in BCVA improvement and CFT reduction for both groups	

achieved a significantly greater reduction of CST compared with the bevacizumab group.³³

The authors of a retrospective study reported DEX implant to be safe and effective over a mean treatment period of 9.8 months. The mean improvement in visual acuity at six months was 7.6 letters. The mean re-injection interval was 5.4 months with on average.³⁴ A prospective study on refractory and naïve DME patients treated with DEX implant and laser as needed reported a significant improvement in VA from baseline (p<0.001) in both groups, especially in the naïve group.³⁵

A retrospective study analysed data of refractory DME patients receiving a single DEX implant. The authors concluded that the DEX implant is effective in difficult-to-treat patients with long-standing

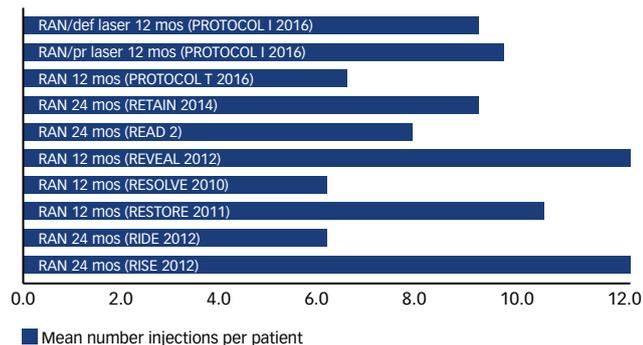
oedema.³⁶ A prospective study in patients unsuccessfully pre-treated with bevacizumab demonstrated that DEX implant significantly increased mean BCVA (logMAR) at one and three months. IOP increases were well controlled with topical anti-glaucoma monotherapy.³⁷ Similar efficacy was reported by Lazic et al. from a prospective dataset in the same patient type.³⁸

A retrospective comparison over six months in vitrectomised versus non-vitrectomised patients with refractory DME reported similar BCVA improvements and reduction of CFT in both groups.³⁹

Discussion

Based on the existing data, VEGF inhibitors as well as corticosteroids have demonstrated efficacy and safety in DME. Furthermore, the use of

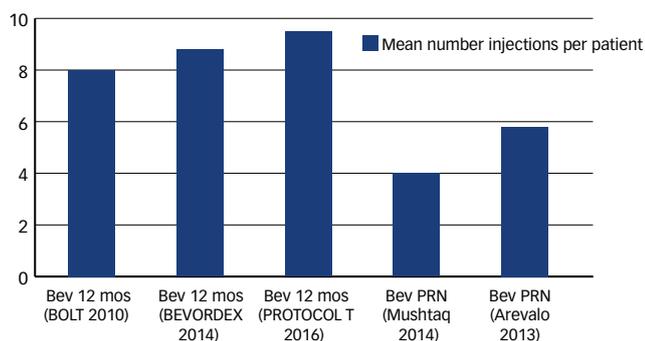
Figure 1: Injection frequency for ranibizumab



VEGF inhibitors are easy to apply and used as treatment of first choice. Based on the recent PROTOCOL T findings, aflibercept seems to achieve better outcomes in eyes with worse baseline VA. An obvious drawback is the high frequency of injection. However, some longer-term data suggest that this frequency is reduced overtime, while still maintaining VA gains previously achieved. Overall, real-world outcomes data do not suggest a lower treatment frequency, if similar efficacy results want to be obtained (Figures 1, 2 and 3).

However, frequent injections increase the number of treatment-related adverse events. Furthermore, they put a great burden on the patient suffering from this chronic disease and decrease patient compliance. Delivery systems can lead to a reduction of these disadvantages.⁴¹

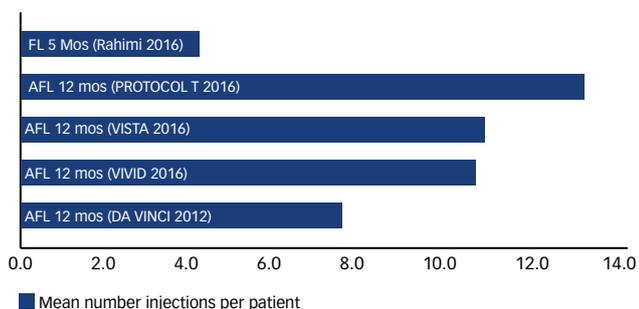
Figure 2: Injection frequency for bevacizumab



Available delivery systems are so far loaded only with corticosteroids. The non-biodegradable delivery system releasing FAc is only available as a last resort option in very restricted patient populations (chronic patients who are resistant to other treatments), with little real-world data currently available. Reasons for this include the long-term nature of the therapy, a potential need to remove the empty device and concerns about lesser control of emerging side effects.

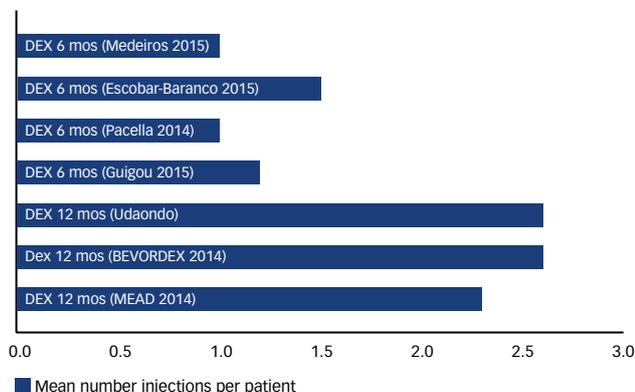
In contrast, DEX implant is indicated in all types of DME for pseudophakic patients or in patients, where alternative treatments are not effective or are inappropriate. The biodegradable implant is injected and does not need to be removed. Compared with anti-VEGF injections, it needs to be administered less often. A fair amount of shorter-term clinical practice data has started to emerge, reporting that treatment intervals remain the same or are slightly shorter or longer. Results suggest a similar to better efficacy compared with the phase III data clinical trial data, and similar efficacy to anti-VEGF. Additional findings suggest that improvement of macular morphology with the DEX implant could be more pronounced. Furthermore, data on combining the DEX implant with anti-VEGF compounds is also emerging.

Figure 3: Injection frequency for aflibercept



Major limitations to comparing pivotal trials with clinical practice data are the differing, mostly shorter study periods, different reporting of efficacy endpoints such as VA, smaller patient numbers and less clearly defined patient populations, especially in respect to duration of DME. Based on the pivotal trial findings, the current assumptions should be that delayed treatment of patients results in lower overall vision gains.

Figure 4: Injection frequency for DEX implant



Apart from injection-related ocular AEs, side-effect profiles between VEGF inhibitors and corticosteroids differ. Main concerns for the latter group revolve around the significant progression of cataract and an increase of IOP. Even though rise of IOP has also been reported in anti-VEGF compounds, this is to a much lesser extent.

A growing concern with intravitreal ranibizumab use in other retinal diseases (such as age-related macular degeneration) is the possible increased risk of occurrence and increased growth of geographic atrophy. Intravitreally applied corticosteroids at low doses have not been observed to exert relevant retinal toxicity.³⁶

Systemic adverse events in general are not associated with corticosteroids, but rather with VEGF inhibitors. There are no consistent reports so far. Non-ocular serious AEs (myocardial infarction, stroke and death) have been reported for ranibizumab in a slightly higher incidence in the treatment than the sham group in studies for DME and other retinal

intravitreal drug delivery in combination with mechanical approaches such as laser therapy show promise for improving visual outcomes and decreasing the need for re-treatment.⁴⁰

diseases (e.g., 2.5% vs. 0.8% in the MARINA study). Cerebrovascular accidents (CVA) occurred in 4% of ranibizumab 0.5 mg patients in RISE and 2.4% of ranibizumab 0.5 mg patients in RIDE. Reported rates of AEs differed amongst studies and groups. However, studies were not powered to detect small differences in rates of infrequent events.⁷ The authors of a recent study comparing outcomes of all VEGF inhibitors in DME propose that due to higher APTC event rates found in ranibizumab, that such events should also be monitored in future.¹² A recent systematic review and meta-analysis of prolonged monthly anti-VEGF use in DME, the assessment of the highest-level exposure group (patients receiving monthly treatment over two years) revealed a possibly increased risk for death and potentially for cerebrovascular accidents. Therefore, the authors concluded that total exposure to anti-VEGF drugs in patients at high risk for vascular diseases should be taken into consideration.⁴²

Conclusions

Management of DME is complex and often multiple treatment approaches are needed. Emerging data on the newly licensed therapies

show VEGF inhibitors and corticosteroids to be equally effective. Corticosteroids appear to be a less treatment-intensive alternative compared with anti-VEGF treatment in DME. While corticosteroids have a widely known safety profile and are already used in well-defined patient populations, recent safety findings on anti-VEGF treatments suggest that there is a need to select patients more carefully.

Currently available datasets scarcely allow direct comparison due to different reporting formats for efficacy and safety parameters, as well as diverging reporting periods. Future real-world data will need to be generated over longer periods of time to inform about long-term treatment efficacy, ideally using uniform reporting parameters to facilitate better comparison of data sets for the same treatment, as well as between treatments.

Future-generation devices should allow even longer release durations and increased target specificity to prolong their action, minimise side effects and achieve patient compliance.⁴³ □

- Holman N, Frouhi NG, Goyder E et al., The Association of Public Health Observatories (APHO) Diabetes Prevalence Model: estimates of total diabetes prevalence for England 2010-2030, *Diabet Med*, 2011;28:575-82.
- Wong TY, Mwamburi M, Klein R et al., Rates of progression in diabetic retinopathy during different time periods: a systematic review and meta-analysis, *Diabetes Care*, 2009;32:2307-13.
- Narayan KM, Boyle JP, Geiss LS, et al., Impact of recent increase in incidence of future diabetes burden, *Diabetes Care*, 2006;29(9):2114-16.
- Early Treatment Diabetic Retinopathy Study Research Group, Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study Report number 1, *Arch Ophthalmol*, 1985;103:1796-806.
- Massin PG, Ranibizumab in diabetic macular edema, Joint Meet Am Acad Ophthalmol Eur Soc Ophthalmol, Atlanta 2008.
- 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;120:2013-22.
- Ford JA, Lois N, Royle P et al., Current treatment in diabetic macular oedema: systematic review and meta-analysis, *BMJ Open*, 2013;3:e002269. Doi:10.1136/bmjopen-2012-002269
- Schmidt-Erfurth U, Lang GE, Holz FG et al., Three-Year Outcomes of Individualized Ranibizumab Treatment in Patients with Diabetic Macular Edema, The RESTORE extension study, *Ophthalmology*, 2014;121:1045-53.
- Googe J, Brucker AJ et al., Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema after focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation, *Retina*, 2011;31:1009-27.
- Elman MJ, Ayala A, Bressler NM et al., Intravitreal Ranibizumab for diabetic macular edema with prompt versus deferred laser treatment. % year randomized trial results, *Ophthalmology*, 2015;122:375-81.
- Bressler SB, Glassman AR, Almkhatar T et al., Five-Year Outcomes of Ranibizumab with Prompt or Deferred Laser versus Laser or Triamcinolone plus Deferred Ranibizumab for Diabetic Macular Edema, *Am J Ophthalmol*, 2016;164:57-68.
- Menchini U, Bandello F, De Angelis V et al., Ranibizumab for Visual Impairment due to Diabetic Macular Edema: Real-world Evidence in the Italian Population (PRIDE Study), *J Ophthalmol*, 2015; doi:10.1155/2015/324841.
- Wells JA, Glassman AR, Ayala AR et al., Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two year Results from a Comparative Effectiveness Randomized Clinical Trial, *Ophthalmology*, 2016, doi: 10.1016/j.ophtha.2016.02.022.
- Michaelidis 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), *Ophthalmology*, 2010;117:1078-86.
- Faghghi H, Roohipoor R, Mohammadi SF et al., Intravitreal bevacizumab versus combined bevacizumab-triamcinolone versus macular laser photocoagulation in diabetic macular edema, *Eur J Ophthalmol*, 2008;18:941-8.
- Lam DS, Lay TY, Lee VY et al., Efficacy of 1.25 MG versus 2.5 MG intravitreal bevacizumab for diabetic macular edema: six-month results of a randomized controlled trial, *Retina*, 2009;29:292-9. doi: 10.1097/IAE.0b013e31819a2d61.
- Ahmadieh H, Ramezani A, Shoebi N et al., Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema; a placebo-controlled, randomized clinical trial, *Graefes Arch Clin Exp Ophthalmol*, 2008;246:483-9.
- Do DV, Nguyen QD, Boyer D et al., One year outcomes in the DA VINCI study of VEGF Trap-Eye in eyes with diabetic macular edema, *Ophthalmology*, 2012;119:1658-65.
- 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;122:2044-52.
- Rahimy E, Shahlaee E, Khan MA, Conversion to aflibercept for persistent DME resulted in significant anatomic improvements. While trends towards improved visual acuity and reduction in IOP were observed, these were not statistically significant, *Am J Ophthalmol*, 2016;164:118-27.
- Campochiaro PA, Brown DM, Pearson A, et al., Sustained delivery of fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema, *Ophthalmology* 2012;119:2125-32.
- 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*, 2014;121:1892-903.
- Elaraoud I, Attawan A, Quhill F, Case Series Investigating the Efficacy and Safety of Bilateral Fluocinolone Acetonide (ILUVIEN®) in Patients with Diabetic Macular Edema, *Ophthalmol Ther*, 2016;Feb 17. [Epub ahead of print]
- Callanan DG, Gupta S, Boyer DS, et al., Dexamethasone intravitreal implant in combination with laser photocoagulation for the treatment of diffuse diabetic macular edema, *Ophthalmology*, 2013;120:1843-50.
- Boyer DS, Faber D, Gupta S, et al., Dexamethasone intravitreal implant for the treatment of diabetic macular edema in vitrectomized patients, *Retina*, 2011;31:915-23.
- Boyer DS, Yoon HY, Belfort R, et al., Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema, *Ophthalmol*, 2014;121:1904-14.
- Augustin AJ, Kuppermann BD, Lanzetta P, et al., Dexamethasone intravitreal implant in previously treated patients with diabetic macular edema: subgroup analysis of the MEAD study, *BMC Ophthalmology*, 2015;15:150.
- 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, *Ophthalmol*, 2014;121:2473-81.
- Fraser-Bell S, Lyndell LL, Campain A et al., Bevacizumab or Dexamethasone Implants for DME: 2 year Results (the Bevordex Study), *Ophthalmology*, 2016;123(6):1399-401.
- Maturi RK, Bleau L, Saunders J et al., A 112-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;35:1604-14.
- Pacella E, La Torre G, Turchetti P, et al., Evaluation of efficacy dexamethasone intravitreal implant compared to treatment with anti-VEGF in the treatment of diabetic macular edema, *Senses Sci*, 2014;1:164-8.
- Shah SU, Harless A, Bleau L, Maturi K, Prospective randomized subject-masked study of intravitreal bevacizumab monotherapy versus dexamethasone implant monotherapy in the treatment of persistent diabetic macular edema, *Retina*, 2016 (published ahead of print; PMID 27124881)
- Guigou S, Pommier S, Meyer F, et al., Efficacy and Safety of Intravitreal Dexamethasone Implant in Patients with Diabetic Macular Edema, *Ophthalmologica*, 2015 DOI:10.1159/000381356.
- Escobar-Barranco JJ, Pina-Marin B, Fernandez-Bonet M, Dexamethasone Implants in Patients with Naive or Refractory Diffuse Diabetic Macular Edema, *Ophthalmologica*, 2015 DOI: 10.1159/000371770.
- Dutra Medeiros M, Postorino M, Navarro R, et al., Dexamethasone intravitreal implant for treatment of patients with persistent diabetic macular edema, *Ophthalmologica*, 2014; 231:141-6.
- Totan Y, Güler E, Güragac FB, Dexamethasone Intravitreal Implant for chronic Diabetic Macular edema Resistant to Intravitreal Bevacizumab Treatment, *Curr Eye Res*, 2015;22:1-7.
- Lazic R, Lukic M, Boras I, et al., Treatment of anti-vascular endothelial growth-factor resistant diabetic macular edema with dexamethasone intravitreal implant, *Retina*, 2014;34:719-24.
- Medeiros MD, Alkabes M, Navarro R, et al., Dexamethasone intravitreal implant in vitrectomized versus nonvitrectomized eyes for treatment of patient with persistent diabetic macular edema, *J Ocul Pharmacol Ther*, 2014;30:709-16.
- The Diabetic Retinopathy Clinical Research Network, Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema, *Ophthalmology*, 2010;117:1064-77.
- Penha FM, Rodrigues EB, Maia M, et al., Retinal and Ocular Toxicity in Ocular Application of Drugs and Chemicals - Part II: Retinal Toxicity of Current and New Drugs, *Ophthalmic Res*, 2010;44(4):205-24.
- Avery LL, Gordon GM, Systemic Safety of Prolonged Monthly Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Macular Edema. A Systematic Review and Meta-analysis, *JAMA Ophthalmol*, 2016;134:21-9.
- Kuno N, Fujii S, Biodegradable Intraocular therapies for Retinal Disorders, *Drugs Aging*, 2010;27(2):117-34.