Diabetic Macular Edema (DME): See the Person Behind the Eye

What everything from basic research to real-world clinical tell us about DME treatment and the impact it has on the macula – and the patient.
**The burden of DME**

From a societal perspective, diabetes is a big problem. Its worldwide prevalence was estimated to be 2.8 percent in 2000, and is projected to reach 4.4 percent by 2030 (1), and the International Diabetes Foundation estimates that nearly 600 million people will have the disease by 2035 (2). It’s associated with many comorbidities, ranging from an increased risk of angina to peripheral neuropathy and leg ulcers. But one of the most pernicious — and one that occurs in 11 percent of all such patients — is diabetic macular edema (DME) (3). Untreated, it can rapidly lead to profound vision loss, and is one of the leading causes of blindness among working-age individuals in industrialized countries (4). Given the demographic trends of a predominantly age-associated eye disease and an aging population, this is a burden that will only get worse for many years to come.

From a patient’s perspective, a DME diagnosis truly can be more than just “a big problem.” In addition to everything else that diabetes can do to a patient, DME massively impacts upon a patient’s quality of life — moreso than asthma, glaucoma or hypertension (5). DME is burdensome too — remember, most patients with DME are managed with intravitreal injections of anti-VEGF agents, which commonly involves monthly clinic visits for assessment and injection (5).

Patients cannot drive after intravitreal injection, so often family members have to take time off work to take them to and from the clinic – which often translates to lost working hours and income for both patient and family. Finally, not everyone responds well to anti-VEGF therapy. Post-hoc analysis of the DRCR.net Protocol I data has shown that BCVA response – after only three anti-VEGF injections – is a strong predictor of long-term BCVA response. So if patients derive insufficient benefit by the third injection, i.e. a gain of ≤5 letters (which comprised 39.7 percent of patients in Protocol I), it’s unlikely that extended therapy will deliver any later additional letter gains (6).

Clearly, a different approach is required to treat these patients (Figure 1).

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**General statistics:**

| **592** | Diabetes projected prevalence: 592 million by 2035 (2) |
| ~11 | percent of diabetes patients get DME (3) |
| >10,000 new cases blindness per year; DME can develop in the first 5 years after diagnosis of Type I diabetes (7) |

A post-hoc analysis of Protocol I showed early response to anti-VEGF agents (by 12 weeks/ three injections) is a strong predictor of BCVA response — even after adjusting for baseline characteristics.

| **39.7** | percent of patients had <5 letter gain by this point (6) |

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| **From the INCITE survey (5):** |
| **75** | percent patients were anxious before their most recent injection treatment |
| **54 percent** were anxious for at least two days prior to treatment and **46 percent** found it hard to think of anything but the injection |
| **53 percent** of patients with jobs needed to take at least one day off work per appointment |
| **50 percent** of carers were employed and 59 percent also needed to take time off work to provide support to the patient |
| **Needing to ask a carer for help led to nearly 30 percent of patients feeling guilty and added to 20 percent of patient’s anxiety levels about their appointment** |

*Patients’ most desired improvement to their treatment regimen was to have fewer injections (42 percent) and fewer appointments (22 percent) to achieve the same visual results.*

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**Figure 1: Key DME statistics**
The molecular history of DME

Why do some patients respond to anti-VEGF therapy well, and others not? Part of the answer may lie in the complex molecular etiology of DME. It is now clear that the main pathologic processes that underpin DME (the disruption of the retinal pigment epithelium [RPE] and the accumulation of fluid in the macula) are the result of multiple disease processes, not one, and we now know that inflammation plays a key role in the early part of this disease (8, 9). Animal studies have shown that diabetes-associated inflammation precedes retinopathy, as does the expression of pro-inflammatory genes (8).

A key strand in the complex web of interactions that starts with hyperglycemia and ends in DME is the disruption of tight junctions between RPE/photoreceptors and their neighboring cells. Rho-associated protein kinase (ROCK) is a protein that plays a key role in regulating cytoskeletal function. Hyperglycemia promotes inflammation, and inflammation-mediated activation of ROCK can lead to cytoskeletal constriction in RPE cells, disrupting RPE cell-Müller cell tight junctions (10). Since one of the functions of Müller cells is to maintain retinal fluid homeostasis, this disruption directly impairs fluid balance and results in edema.

Another consequence of inflammation in the very early phase of diabetes is microglial activation and accumulation (11, 12). Under normal circumstances, activated microglial cells migrate out of the retina via transcellular pathways, which allow the cells to exit the retina without disrupting tight junctions. These pathways rely on the formation of specific pores – but in diabetes, this pore protein is inactivated by abnormal glycosylation (11). The result: inadequate clearance and accumulation of activated microglial cells from the retina, where they go on to release pro-inflammatory cytokines and further exacerbate a growing inflammatory micro-environment in the retina.

Many other factors also contribute to DME: for example, capture of leukocytes by inflamed endothelium; release of inflammatory cytokines by these leukocytes; an inflammatory cascade; VEGF release and subsequent neovascularization (13–15). The key point, however, is that the release of inflammatory mediators is a very early event in the development of DME, and VEGF is only one of many mediators involved (8, 13; Figure 2).

“Inflammation happens much earlier in the process than we’d appreciated.”
Baruch Kuppermann
Figure 2. Molecular natural history of DME. Inflammation is a very early event in the development of DME. It precedes retinopathy, and is the result of many interactions between multiple factors, of which VEGF is but one. Although VEGF is upregulated, its expression remains relatively constant as retinopathy develops, whereas all other inflammatory factors continue to increase dramatically as retinopathy proceeds.
This understanding of DME etiology helps explain real-world responses to DME pharmacotherapy. Analysis of the DRCR.net’s Protocol I data has shown that BCVA response after three injections is a strong predictor of long-term BCVA response – and at that this point, 39.7 percent of patients displayed <5 letter BCVA gains (6). This variation in response might be explained by the existence of two distinct processes involved in the development and progression of DME: VEGF-mediated vascular permeability, the other, inflammation-mediated (13). Single (off-label) intravitreal injection of the steroid triamcinolone has been shown to dramatically reduce the concentration of many pro-inflammatory cytokines assessed, including VEGF (by around 80 percent; Figure 3) (13). As we know that pro-inflammatory cytokine levels continue to increase as DME progresses, it’s therefore possible that there is a proportion of patients with DME where the disease process is no longer primarily mediated by VEGF (16).

There are certainly many reasons to expect patients with DME to respond well to steroids: they inhibit inflammatory prostaglandins, modulate

![Figure 3. Steroids address the multifactorial nature of DME. Pre- and post-injection levels of pro-inflammatory/ pro neovascularization cytokines after bilateral injection of IVTA (one eye; n=11) and IVB (the other eye; n=11) in patients (n=11) with DME. *Wilcoxon signed rank test. IL, interleukin; IP, interferon-inducible protein; IVT, intravitreal triamcinolone acetonide; IVB, intravitreal bevacizumab; MCP, monocyte chemotactic protein; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor. Adapted from (13).]
Figure 4. Comparison of deep capillary plexus in poor-responding vs. responding DME patients. The superficial capillary plexi do not differ significantly between anti-VEGF therapy poor-responders and responders; in contrast, the non-responder deep capillary plexi score relatively poorly on all criteria. Data courtesy of Young Hee Yoon, Professor of Ophthalmology, Asan Medical Centre, University of Ulsan, Seoul, Korea; adapted from [20]).

The dexamethasone implant reduces macular thickness and improves functional outcomes.”
Borja Corcóstegui

<table>
<thead>
<tr>
<th></th>
<th>Poor-responder DME (n = 51)</th>
<th>Good-responder DME (n = 32)</th>
<th>P Value</th>
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<tr>
<td>SCP</td>
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<tr>
<td>Mean number of MAs (SD)</td>
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<td>0.3 (0.7)</td>
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<tr>
<td>Mean VFD, %</td>
<td>21.81 (3.71)</td>
<td>21.94 (3.34)</td>
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<tr>
<td>Mean FAZ area (SD), mm²</td>
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<td>0.954</td>
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<tr>
<td>DCP</td>
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<td></td>
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<tr>
<td>Mean number of MAs (SD)</td>
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<td>3.9 (1.2)</td>
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<td>0.87 (0.41)</td>
<td>0.57 (0.22)</td>
<td>&lt; 0.001</td>
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</tbody>
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The activation of immune cells, and also inhibit ROCK activity (17–19) – all of which could help prevent the very early events that lead to tight junction disruption.

What does this mean for the clinic? Analysis of the Protocol I clinical trial data (6) has shown that BCVA response (after only three anti-VEGF injections) is a strong predictor of long-term BCVA response, and by this time point, 39.7 of patients exhibited a BCVA gain of <5 letters, and this suggests that there is a group of patients who might not gain letters. Wouldn’t it be nice to know right from the start, so that other treatment options – like steroid therapy – could be explored? It turns out that microaneurysm turnover and deep capillary plexus integrity as assessed by OCT angiography might act as a predictive biomarker – as to whether a patient responds well (or not) to anti-VEGF drugs (Figure 4) – and help individualize and optimize the patients’ therapeutic regimen (20).
Often a drug does not perform as well in the real world as it does in clinical trials (21). Regimen adherence is closely monitored in trials, and outcomes are intensively and closely monitored – but that level of scrutiny just isn’t feasible in the real world. One example is the AURA study (22), where its investigators examined the real-world use of an anti-VEGF agent, in this case, ranibizumab, for the treatment of wet age-related macular degeneration – a landmark study. They found that patients in the real world failed to achieve outcomes that were anything like those achieved in phase III clinical trials, with inadequate monitoring compromising treatment regimens being identified as a likely cause.

The same pattern of apparent underutilization can be seen when DME anti-VEGF clinical use and outcomes data are compared with prospective pivotal trial data. The large clinical trials of anti-VEGF therapy for the treatment of DME suggest that better visual acuity comes with more frequent injections – RESOLVE (23), RISE/RIDE (24) and DRCR.net Protocol T (25) utilized more frequent injection regimens and achieved greater mean numbers of letters gained over 12 months than studies like RESTORE (26) or DRCR.net Protocol I (27) which employed less-frequent pro re nata dosing regimens. For example, in RESOLVE, an average of 10.2 injections was associated with a mean +10.3-letter gain (compared with -1.4 letters for sham group), whereas RISE/RIDE employed monthly injections with a +10.9/+12.5 mean letter gain (with the 0.3 mg ranibizumab dose; this compares with +2.3 /+2.6 for the sham groups) and Protocol T averaged between nine and 10 injections across the aflibercept, bevacizumab and ranibizumab groups with overall letter gains ranging from +9.7 to +13.3 in the first year – but in RESTORE, patients averaged only 6.8 to 7.3 injections with a +6.4 to +6.8 letter gain (versus +0.9 for the laser-only group). In Protocol I, patients in the injection or injection plus prompt laser averaged nine and eight injections respectively, with a +9.0 letter gain in both groups. But in the real world, the number of injections these patients receive is considerably lower – one claims analysis (28) found that newly-diagnosed patients with DME received
between 2.2 and 3.6 injections per year – most unlike the numbers noted in the trials above.

Under-treatment may arise from poor compliance on the part of the patient, but also from dosing approaches such as treat-and-extend or pro re nata. In particular, where a clinic’s resources are limited, there may be some temptation to overuse treat-and-extend, which is said to result in 46 percent fewer clinic visits (29, 30).

The dexamethasone-containing extended-release intravitreal implant, exhibited comparable efficacy in its Phase III clinical trial (MEAD [31]) as in real life, per the results of the Reldex study (32) – a three year retrospective follow-up of patients who received the dexamethasone intravitreal implant. This compares well with MEAD (22 percent). Likewise, real-world data presented by Young Hee Yoon (20) indicate that in 35 anti-VEGF poor responders treated with dexamethasone implants (Figure 5), 76 percent of eyes achieved a central retinal thickness (CRT) reduction of ≥100 µm.

Patricia Udaondo (Department of Medical Ophthalmology, New University and Polytechnic Hospital La Fe, Valencia, Spain) also confirms the real-world utility of the dexamethasone intravitreal implant, describing her own safety and efficacy analysis of data from 73 DME patients (110 eyes) treated with the implant. “Dexamethasone use was associated with a reduction in macular thickness and improved functional outcomes: 53 percent of patients showed a gain of 10 letters or more, and 40 percent showed a visual gain of three lines or more” (33). And Borja Corcóstegui (Medical Director, Institute for Ocular Microsurgery, Barcelona, Spain) describes a 62 year old man who had had diabetic retinopathy for 31 years. “His visual acuity dropped to 4/10. Five years after starting therapy with the dexamethasone intravitreal implant, he reached 20/25 visual acuity, using two implants per year” Corcóstegui adds that on occasions where cataracts development did occur, it was resolved with cataract surgery and IOL implantation (33).

What about real-world safety? Udaondo found that: “Under 20 percent of patients had an IOP increase of >10 mmHg and only 3.5 percent had an important IOP increase (up to 30 mmHg). However, 36 percent required cataract surgery” (33).

“Reldex showed that dexamethasone mediates an average gain of 9.5 letters at three years” Laurent Kodjikian”
Kodjikian also collected adverse event data and has particular insights with regard to cataract incidence. “Note that 70 percent of cataract surgery was required after the first injection – i.e. most DME patients already had advanced cataracts before implantation.” He personally experienced no glaucoma or sustained hypertension after patients stopped receiving, and of the patients who needed treatment for ocular hypertension developed during the study, 96 percent required only topical therapy to control (33).

Kodjikian also points to data from the Reldex study indicating that patients who are treated with the dexamethasone intravitreal implant show no significant visual impairment after cataract surgery (32). He ascribes this to the timing of the injection. “Most injections were given in the month before cataract surgery – so there was less DME at the time of surgery, and the steroid implant repressed inflammation during and after surgery” (32).

What can we conclude from these experts’ real life experiences? Kodjikian puts it like this: “The dexamethasone intravitreal implant places less burden on patients and clinics.”
Deriving benefit

Who might benefit from switching to the dexamethasone intravitreal implant? Post-hoc analysis of Protocol I has shown that at 12 weeks (after three injections), the enrolled patient population could be categorized into three groups: 39.7 percent, 23.2 percent and 37.1 percent demonstrated BCVA improvements of <5, 5–9 and ≥10 letters, respectively, in response to anti-VEGF treatment – and this response at 12 weeks predicted their overall long-term response to anti-VEGF therapy. What do you do with patients that exhibit an insufficient response (<5 letter BCVA gain)? Dugel et al.’s conclusion was “Additional therapies with alternative modes of action may be considered in inadequately responsive DME patients after three injections” (6).

Diabetes is a pro-inflammatory state (35) and inflammation is an early, central and constant component of DME pathogenesis. We know that VEGF is only one of many pro-inflammatory cytokines upregulated in DME, and that VEGF inhibitors inhibit just one of these cytokines, whereas steroids inhibit many. The question is, how long is it reasonable to wait to administer steroid therapy in patients diagnosed with DME?
References


33. DAtion file, Allergan Inc.


OZURDEX® (Dexamethasone 700 micrograms intravitreal implant in applicator)

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Allergan.

Abbreviated Prescribing Information

Presentation: Intravitreal implant in applicator. One implant contains 700 micrograms of dexamethasone. Disposable injection device, containing a rod-shaped implant which is not visible. The implant is approximately 0.46 mm in diameter and 6 mm in length. Indications: Treatment of adult patients: with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO), inflammation of the posterior segment of the eye presenting as non-infectious uveitis and visual impairment due to diabetic macular oedema (DME) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy. Dosage and Administration: Please refer to the Summary of Product Characteristics before prescribing for full information. OZURDEX must be administered by a qualified ophthalmologist experienced in intravitreal injections. The recommended dose is one OZURDEX implant to be administered intra-vitreally to the affected eye. Administration to both eyes concurrently is not recommended. Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician’s opinion may benefit from retreatment without being exposed to significant risk. Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by OZURDEX, should not be retreated. In RVO and uveitis there is only very limited information on repeat dosing intervals less than 6 months. There is currently no experience of repeat administrations in posterior segment non-infectious uveitis or beyond 2 implants in Retinal Vein Occlusion. In DME there is no experience of repeat administration beyond 7 implants. Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs. Single-use intravitreal implant in applicator for intravitreal use only. The intravitreal injection procedure should be carried out under controlled aseptic conditions as described in the Summary of Product Characteristics. The patient should be instructed to self-administer broad spectrum antimicrobial drops daily for 3 days before and after each injection. Contraindications: Hypersensitivity to the active substance or to any of the excipients. Active or suspected ocular or periorcular infection including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases. Advanced glaucoma which cannot be adequately controlled by medicinal products alone. Aphakic eyes with ruptured posterior lens capsule. Eyes with Anterior Chamber Intraocular Lens (ACIOL), iris or transscleral fixated intraocular medicinal products alone. Aphakic eyes with ruptured posterior lens capsule. Eyes with a history of vitrectomy, are at risk of implant migration into the anterior chamber. Risk of implant migration to the anterior chamber may lead to corneal oedema. Persistent severe corneal oedema could progress to the need for corneal transplantation. Other than those patients contraindicated where OZURDEX should not be used, OZURDEX should be used with caution and only following a careful risk benefit assessment. These patients should be closely monitored to allow for early diagnosis and management of device migration. Use of corticosteroids, including OZURDEX, may induce cataracts (including posterior subcapsular cataracts), increased IOP, steroid induced glaucoma and may result in secondary ocular infections. The rise in IOP is normally manageable with IOP lowering medication. Corticosteroids should be used cautiously in patients with a history of ocular herpetic simplex and not be used in active ocular herpetic simplex. OZURDEX is not recommended in patients with macular oedema secondary to RVO with significant retinal ischemia. OZURDEX should be used with caution in patients taking anti-coagulant or anti-platelet medicinal products.

Interactions: No interaction studies have been performed. Systemic absorption is minimal and no interactions are anticipated. Pregnancy: There are no adequate data from the use of intravitreally administered dexamethasone in pregnant women. OZURDEX is not recommended during pregnancy unless the potential benefit justifies the potential risk to the foetus. Lactation: Dexamethasone is excreted in breast milk. No effects on the child are anticipated due to the route of administration and the resulting systemic levels. However OZURDEX is not recommended during breast-feeding unless clearly necessary. Driving/Use of Machines: Patients may experience temporarily reduced vision after receiving OZURDEX by intravitreal injection. They should not drive or use machines until this has resolved. Adverse Effects: In clinical trials the most frequently reported adverse events were increased intraocular pressure (IOP), cataract and conjunctival haemorrhage. Increased IOP with OZURDEX peaked at day 60 and returned to baseline levels by day 180. The majority of elevations of IOP either did not require treatment or were managed with the temporary use of topical IOP-lowering medicinal products. 1% of patients (4/347 in DME and 3/421 in RVO) had surgical procedures in the study eye for the treatment of IOP elevation. The following adverse events were reported: Very Common (≥1/10): IOP increased, cataract, conjunctival haemorrhage. Common (≥1/100 to <1/10): headache, ocular hypertension, cataract subcapsular, vitreous haemorrhage, visual acuity reduced, visual impairment/disturbance, vitreous detachment*, vitreous floaters*, vitreous opacities*, blepharitis, eye pain*, photopsia*, conjunctival oedema*, conjunctival hyperaemia. Uncommon (≥1/1,000 to <1/100): migraine, necrotizing retinitis, endophthalmitis*, glaucoma, retinal detachment*, retinal tear*, hypopyon of the eye*, anterior chamber inflammation*, anterior chamber cells/flares*, abnormal sensation in eye*, eyelids pruritus, scleral hyperaemia*, device dislocation* (migration of implant) with or without corneal oedema, complication of device insertion* (implant misplacement). (Adverse reactions considered to be related to the intravitreal injection procedure rather than the dexamethasone implant). Please refer to Summary of Product Characteristics for full information on side effects. Basic NHS Price: £870 (ex VAT) per pack containing 1 implant. Marketing Authorisation Number: EU/1/10/638/001. Marketing Authorisation Holder: Allergan Pharmaceuticals Ireland, Castlebar Road, Westport, Co. Mayo, Ireland. Legal Category: POM. Date of preparation: September 2016

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