Long-term Therapies for Diabetic Macular Edema

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Abstract

Diabetic macular edema (DME) is one of the main causes of visual loss in diabetic patients. Although photocoagulation and intensive control of systemic metabolic factors have achieved improved outcomes, improvement is slow and some patients with DME continue to lose vision despite treatment. Pharmacological treatment options for DME include vascular endothelial growth factor (VEGF) antagonists such as ranibizumab, bevacizumab and pegaptanib and corticosteroids, whose multiple mechanisms of action include reduction of VEGF expression. Intravitreal delivery of these agents has shown efficacy in the treatment of DME but is associated with adverse effects including cataract progression and sustained rises in intraocular pressure. The physical characteristics and potent anti-inflammatory properties of fluocinolone acetonide (FAc) have led to its use in intravitreal implants. A number of intravitreal implants have been evaluated, of which the most effective at providing sustained drug release with an acceptable safety profile is the ILUVIEN® implant. This FAc intravitreal implant provides significant, long-lasting improvements in visual acuity for patients with chronic DME and has a manageable safety profile.

Keywords

Corticosteroids, diabetic macular edema, fluocinolone acetonide, ILUVIEN®, intravitreal implant

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Diabetic retinopathy is the leading cause of blindness among patients 20 to 70 years old in developed countries. Diabetic macular edema (DME) can develop at any stage of diabetic retinopathy and is a major cause of preventable vision loss. It is also a public health concern, given the increasing prevalence of diabetes.[1–3] A recent pooled individual participant meta-analysis estimated that there are 21 million people with DME worldwide with an overall prevalence of 6.81 % among individuals with diabetes.[4] The prevalence is higher in those with type 1 than with type 2 diabetes.

The pathogenesis of DME involves overlapping and inter-related pathways initiated by hyperglycaemia. These are responsible not only for vascular events, but also in continued tissue insult that result in chronic DME. Angiogenesis, inflammation and oxidative stress lead to hyperpermeability, disruption of vascular endothelial cell junctions and leukostasis.[5] Diabetes generally becomes more inflammatory with duration, and there is growing evidence that the levels of inflammatory cytokines increases with duration of DME. Retinal hypoxia has been implicated in DME pathogenesis and stimulates vascular endothelial growth factor (VEGF) transcription.[5–11] VEGF increases retinal vascular permeability, causes breakdown of the blood–retina barrier and results in retinal edema.[12] It is up-regulated in diabetic retinopathy, making it an important therapeutic target in DME. However the products of other hypoxia-inducible genes, such as placental growth factor[13] and hepatocyte growth factor,[12–14] also induces the influx of leukocytes into the retina which can cause vascular leakage, hypoxia or ischaemia.

Laser photocoagulation, which is the current standard of care, results in slow improvement in a minority of patients. Furthermore, some patients suffer permanent visual loss even after intensive treatment.[15,16] Visions worsen in approximately 20 % of laser-treated patients after two years,[17] following ranibizumab combined with laser treatment, 30 % show a halving of their visual angle.[18] The control of systemic metabolic factors can minimise visual loss. In patients unresponsive to standard laser techniques, pharmacological treatment may be beneficial in addition to improving control of blood pressure and blood sugar. The aim of this article is to review the current pharmacological treatment options for DME, particularly the use of intravitreal implants.

Treatment of DME

Over the last few years, research has focused on the use of VEGF antagonists to treat DME. Intraocular injections of ranibizumab or bevacizumab targeting VEGF result in rapid reduction of edema and improvement in visual acuity (VA) in patients with DME. Ranibizumab has recently been approved by the European Medicines Agency (EMA) for the treatment of vision impairment due to DME, following a number of clinical trials: the Phase II REVEAL trial (n=151),[19] the Phase II READ-2 study (n=126),[20] the Phase II RESOLVE study[19] and the Phase III RESTORE trial (n=345, 12 months).[21] All resulted in significant increases in VA and reductions in retinal thickness. The READ-2 and RESTORE studies demonstrated superiority over laser treatment. A larger Phase III trial (854 study eyes of 691 participants) demonstrated the efficiency and safety of ranibizumab over two

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years.[22] Study data show that the efficacy of these anti-VEGF monoclonal antibody treatments is related to the number and frequency of injections.[23] To date, less evidence is available to support the use of bevacizumab in DME, although recent data from the Phase II study BOLT-2 (n=80) indicates that improvements in VA and reductions in retinal thickness seen at one year are maintained at two years.[24,25] Pegaptanib sodium is another anti-VEGF agent that has shown efficacy in the treatment of DME, as demonstrated in a recent Phase II/III trial (n=467).[26]

While the efficiency and safety of the intravitreal use of anti-VEGF agents has been established, suppression of inflammatory mediators and other permeability factors in addition to VEGF is a more comprehensive treatment strategy for DME. This provides a rationale for the use of corticosteroids. Corticosteroids act at both biochemical and anatomical levels to exert their therapeutic actions; they not only reduce VEGF expression and permeability factors in the eye, but also suppress inflammation and leukocyte influx to the retina. A number of corticosteroids have been shown to inhibit the expression of VEGF and various agents are being used off-label or are in clinical trials to treat DME (see *Table 1*). The corticosteroid budenoside inhibits VEGF expression in a retinal pigment epithelial cell line through the glucorticoid receptor.[27] Intravitreal injection of dexamethasone in DME-induced rats reduces vascular permeability and leukostasis and downregulates intercellular adhesion molecule-1 (ICAM-1) mRNA expression.[28] Dexamethasone also reduces VEGF mRNA levels and ICAM-1 expression in diabetic rats.[29]

Since it was first introduced in the 1970s, the use of intravitreal injection of triamcinolone acetonide (IVTA) has become more frequent in ophthalmic practice to treat macular edema. IVTA is effective at reducing macular thickness and increasing VA in patients with DME; however it provides only short-term visual improvement.[30] Furthermore, multiple injections are required and intraocular injections are associated with complications similar to intravitreal surgery, including haemorrhage, retinal detachment, and endophthalmitis.[31] In a prospective randomised trial to compare the safety and efficiency of different doses of IVTA in treating DME, the mean best-corrected VA (BCVA) improvement at six months was significantly higher for patients receiving 8 mg IVTA compared with the group receiving 4 mg. However, ocular hypertensive responses occurred in 55 % of eyes in the 8 mg group.[32] A dose-escalation study of IVTA showed that both doses of IVTA were well tolerated and led to significant improvements in VA in the short term, but a rise in intraocular pressure (IOP) of ≥10 mmHg occurred in 41 % in the 4 mg group.[33]

In a prospective, double-masked, placebo-controlled clinical trial of eyes with DME and impaired vision (≤20/40) randomised to IVTA 4 mg versus placebo six weeks before laser treatment, visual outcomes and the need for further laser treatment at six months were no better in the IVTA group than in the laser-alone group, despite a reduction in mean central macular thickness in the treatment group.[34] Furthermore, a three-year follow-up of a randomised trial comparing laser therapy with intravitreal triamcinolone for DME showed significantly improved visual outcomes in the laser-treated group compared with IVTA.[17, 35] In a Phase II trial of IVTA in patients with mild DME, there were no significant changes in VA and retinal thickness at 34 weeks.[36] The study concluded that a Phase III trial could not be justified and that it is unlikely that there is a meaningful clinical benefit for IVTA in cases of DME with good VA.

Table 1: Selected Clinical Studies of Corticosteroids in Diabetic Macular Edema Therapy

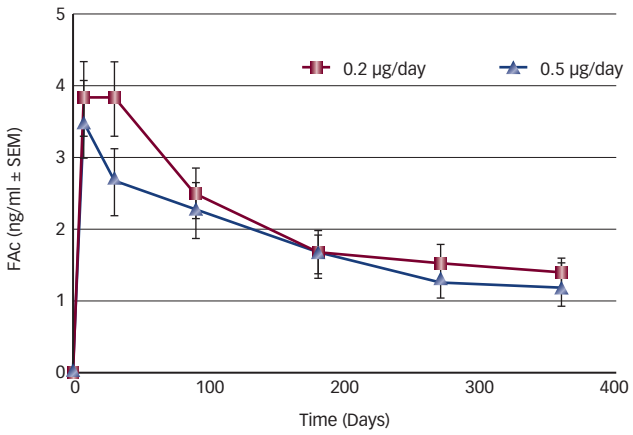
Agent	Number of Patients	Main Outcomes	Reference
Intravitreal triamcinolone (IVTA)	693	Less favourable results versus photocoagulation at 24 and 36 months	17, 35
Dexamethasone drug delivery system (Ozurdex)	171	Generally favourable outcomes at 90 days	41
Fluocinolone acetonide implant (Retisert)	197	Effective DME therapy at 36 months, however high risks of cataract and glaucoma	44, 49
Fluocinolone acetonide implant (ILUVIEN)	956	Generally favourable outcomes at 36 months	54

Table 2: Comparison of Intravitreal Corticosteroid Products[38]

Agent	Total Dose (Daily Release)	Procedure	Duration
Posurdex®	750 µg dexamethasone (estimated~6.25 µg/day)	Injectable	~4 months
IVTA (Triesence™, Trivaris™)	4 mg TA (unknown)	Injectable	~3 months
Retisert®	500 µg FA (0.59 µg/day)	Incision and suture	2.5 years
Iluvien™	180 µg (0.5 µg or 0.2 µg/day)	Injectable	Up to 3 years
I-Vation™	Dose 925 µg TA	Incision with scleral implantation	Up to 2 years

FA = Fluocinolone acetonide; TA = Triamcinolone acetonide; IVTA = Intravitreal injection of triamcinolone acetonide.

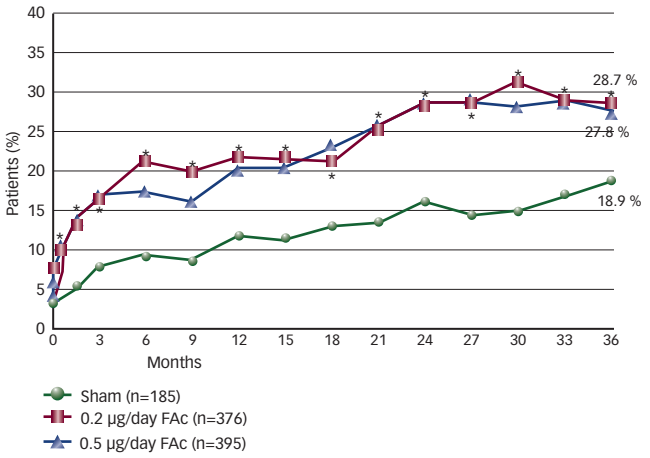
Figure 1: Mean Aqueous Levels of Fluocinolone Acetonide (FAc) in Patients with Persistent Diabetic Macular Edema at Time Points After Receiving Intraocular Implants Releasing 0.2 or 0.5 µg/day[53]



Intravitreal Implants

As a result of the lack of sustained efficacy of intravitreal administration of corticosteroids, recent research has focused on sustained-release intravitreal implants containing anti-VEGF agents. Sustained drug delivery systems release low doses over a long period, avoiding frequent repeated injections and wide fluctuations in intraocular corticosteroid concentrations.[37] In the last decade, intravitreal implants have been developed that show superior duration of treatment compared

Figure 2: Vision Outcomes Through 36 Months in Patients with DME Treated with 0.2 or 0.5 µg/day FAc Implants versus Sham Injection in the FAME Study[52] – Percentage of Patients with an Increase of ≥15 Letters in BCVA (LOCF)



BCVA = best-corrected visual acuity; DME = diabetic macular edema; FAc = fluocinolone acetonide; FAME = fluocinolone acetonide for macular edema study; LOCF = last observation carried forward.

with intravitreal injection (see *Table 2*).[38] A triamcinolone acetonide (TA)-eluting device, I-vation (SurModics, Inc), was suspended in a Phase II trial following publication of data comparing laser treatment with intravitreal injections of TA.[39]

The dexamethasone drug delivery system (DDS; Ozurdex, Allergan) is a biodegradable, sustained-release device approved by the US Food and Drug Administration (FDA) and by the EMA for the treatment of macular edema associated with retinal vein occlusion and non-infectious posterior segment uveitis. A Phase II trial in patients with persistent macular edema secondary to various aetiologies including DME (n=315) found that the dexamethasone system produced improvements in VA, macular thickness and fluorescein leakage that were sustained for up to six months.[40] In a further study of patients with persistent DME (≥90 days' duration), treatment with the intravitreal dexamethasone DDS was well tolerated and produced significant improvements in VA, central retinal thickness and fluorescein leakage compared with an observation group. However these improvements were no longer statistically significant at six months.[41] Moreover, the efficacy of this implant has not been established beyond six months. Further study is needed to determine the actual duration of clinical benefit and when retreatment might be appropriate.

Fluocinolone acetonide (FAc) has anti-VEGF properties[42,43] and its physical characteristics and potent anti-inflammatory properties make it a good choice for these systems. FAc is more lipophilic than triamcinolone acetonide and dexamethasone and therefore should have a more effective posterior clearance route and cause fewer problems with ocular hypertension.[44] It has been shown that FAc can inhibit VEGF expression in a retinal pigment epithelial cell line and reduce proliferation.[42]

Retisert (Bausch and Lomb) is a device sutured to the anterior eye wall that releases 0.59 µg/day FAc into the anterior part of the vitreous cavity and has shown efficacy in the treatment of chronic non-infectious posterior uveitis.[45,46] A four-year multicentre clinical trial found that the intravitreal implant significantly improved VA and diabetic retinopathy severity score (DRSS) and reduced DME. However common adverse effects included cataract progression, elevated IOP, vitreous haemorrhage, and abnormal sensation in the eye. Elevations in IOP increased with time and could not be managed with IOP-lowering medication resulting in 20 % of patients requiring open incision glaucoma surgery within two years. By four years, 91 % of implanted eyes had cataract extraction and 33.8 % required surgery for ocular hypertension.[44,47–50]

ILUVIEN® (Alimera Sciences), a novel FAc intravitreal implant, is a smaller non-biodegradable cylindrical tube with the same activity as Retisert that does not require surgical implantation. Instead, the device can be inserted into the vitreous cavity through a 25-gauge applicator in an outpatient setting. Two devices releasing two doses of FAc (0.5 or 0.2 µg/day) *in vitro* have been developed.[38] It was hypothesised that these implants may cause fewer problems with glaucoma than the surgically implanted devices because of lower *in vitro* release rates of FAc and also because of a more posterior location in the eye.[44]

The open-label Phase II Pharmacokinetic and Efficiency Study of Fluocinolone Acetonide Implants in Patients with DME (FAMOUS) study (n=37) showed that FAc implants provided excellent sustained intraocular delivery for at least one year and reduced DME (see *Figure 1*). There was a mild increase in mean IOP after administration of 0.5 µg/day implants, but not after administration of 0.2 µg/day implants.[51-53] The subsequent Fluocinolone Acetonide for diabetic Macular Edema (FAME) study (n=953) comprised two parallel Phase III studies and tested the effects of FAc implants in patients with persistent DME despite at least one macular laser photocoagulation treatment. As a result, this study allowed for the evaluation of continuous, low-dose, corticosteroid exposure in a population, which included patients with chronic edema, which had not been done in other Phase III trials. Patients in the treatment groups showed significant reduction in foveal thickness at all time points compared with sham injection. Both low-dose (0.2 µg/day) and high-dose (0.5 µg/day) implants significantly improved VA. The results of this study suggest that the release rate of steroid within the eye is critical and can be altered in a way to minimise toxicity while maintaining benefit. The low- and high-dose implants showed no significant difference in efficacy, but significantly fewer incisional IOP lowering procedures were needed in the low-dose group and patients receiving the low-dose implants experienced fewer IOP increases at any time point compared with the high-dose patients. The majority (61.6 %) of patients treated with the 0.2 µg/day implant did not require IOP-lowering medication and <5 % required IOP-lowering surgery. In patients with chronic DME, the benefit-to-risk ratio was doubled.[54] The FAME trial results also suggested that in year three, anatomy is more strongly associated to function in patients with non-chronic DME versus chronic DME. The implications of this finding require further research.

A long-term study confirmed the efficacy and safety of FAc implants in patients with visual impairment from centre-involved DME having at least one prior macular laser treatment, over a three-year follow-up period. Sustained follow-up of the FAME study demonstrated that the positive outcomes were maintained through at least three years, with approximately 28 % of patients in the FAc implant groups still demonstrating improvement of ≥15 in BCVA letter score (see *Figure 2*).[52]

The impact of duration of DME on visual outcome was assessed in a pre-planned subgroup analysis. Patients who entered the FAME study had a median duration of DME of three years. In the chronic DME population (duration >=three years), a significant additional benefit was seen with the 0.2 µg/day implant, versus the control group who were receiving laser treatment, intravitreal steroids and anti-VEGF agents according to the recommendation of a masked, assessing physician. Thus, the controls were receiving treatments comparable to standard of care. This additional benefit of FAc treatment is striking compared with the non-chronic population, which was also receiving standard of care, but, the addition of the 0.2 µg/day implant did not add additional benefit. Interestingly, the anatomic status of both the control groups, and the 0.2 µg/day implant groups are similar at month 36 in both the chronic and nonchronic populations, however, as seen in *Figure 3*, the functional status at month 36 was very different for these two groups in the chronic population.[52]

The superior outcomes occurred despite a high incidence of cataract requiring surgery in patients who received a FAc implant. Patients in the FAc groups who required cataract surgery had a mean increase in BCVA letter score of seven, a similarly good result as those patients who were pseudophakic at baseline, mean improvement of six.[52]

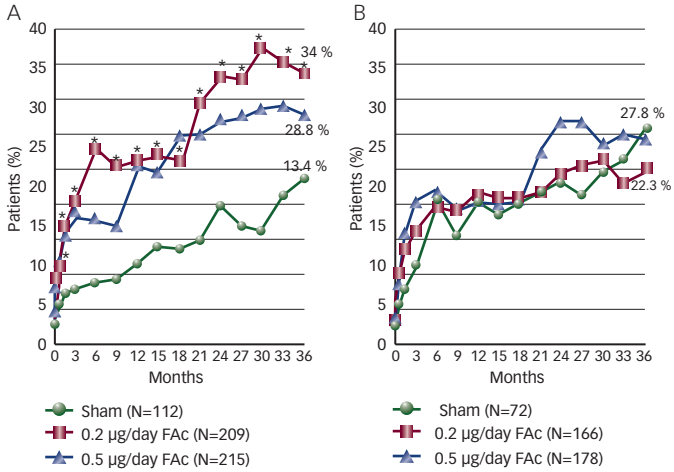
The percentage of patients that required incisional glaucoma surgery was 8.1 % in the 0.5 µg/day FAc group and 4.8 % in the 0.2 µg/day FAc group. FAc implants also caused regression of diabetic retinopathy grade with a smaller percentage of patients with ≥2 step improvement on the Early Treatment Diabetic Retinopathy Study retinopathy scale at 36 months in the sham treatment group (8.9 %) than the 0.2 µg/day FAc group (13.7 %); the 0.5 µg/day FAc was similar to the sham (10.1 %) (see *Figure 4*).[52]

Future Developments

Although at present the use of intravitreal implants is not recommended as first-line therapy, the impending requirement for cataract surgery in a patient with DME may be a rationale to consider an intravitreal implant as a therapy option for patients who have not benefited from laser photocoagulation. In the 24-month outcomes from the clinical trial of IVTA plus laser versus laser treatment only in eyes, it was found that 61 % of patients with DME undergoing IVTA required cataract removal versus 0 % of patients receiving laser therapy only after two years.[55] Cataract progression was observed in approximately 43 % of patients implanted with Retisert after one year.[44] Cataract removal was required in 91 % of phakic eyes within four years. In the FAME study phakic population, cataract surgery was performed in 80 % of the 0.2 µg/day FAc group, 87 % of the 0.5 µg/day FAc group, and 27 % of the sham group. The visual benefit for the patients who received the FAc implant was similar between the patients who entered the study phakic and became pseudophakic and those who entered the study pseudophakic.[52]

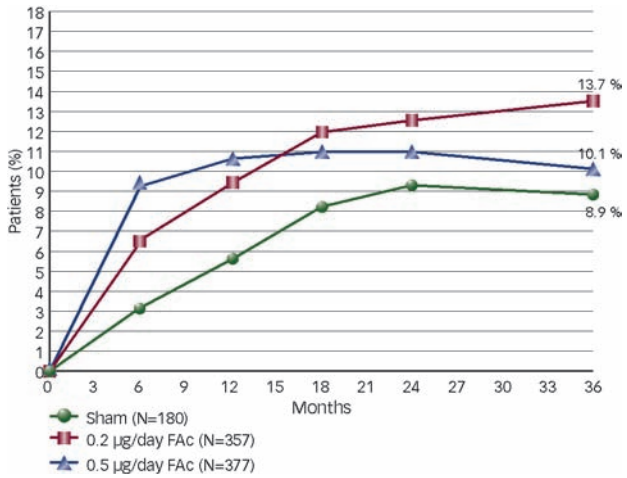
Corticosteroid treatment is associated with an increase in IOP in some patients leading to a risk of optic nerve damage and glaucoma.[56-58] This is a result of greater outflow resistance from the trabecular meshwork that is ascribed to various mechanisms including increased secretion of fibronectin and other factors.[59] This effect is more prevalent with corticosteroid treatments applied topically to the eye and eyelids but to a lesser extent is also associated with systemic treatment. IOP increases resulting from corticosteroid treatments are more common in patients with a history of glaucoma or elevated IOP, in very young

Figure 3: Subgroup Analysis: Visual Outcome in Patients with DME Treated with 0.2 or 0.5 µg/day Fluocinolone Acetonide (FAc) Implants Versus Sham Injection in the FAME A+B trial.[52] A) Patient with DME ≥3 Years at Baseline, B) Patients with DME <3 Years at Baseline as Determined by Increase of ≥15 Letters in BCVA



BCVA = best-corrected visual acuity; FAME A + B = Fluocinolone Acetonide for Macular Edema trial.

Figure 4: The Percentage of Patients with 2-step Improvement in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Score[52]



FAc = fluocinolone acetonide.

or elderly patients, and with connective tissue disease or keratoplasty.[58] Dexamethasone and prednisolone are more likely to result in IOP increases than other corticosteroids such as fluoromethalone, hydrocortisone, and rimexolone. In most patients with such IOP elevations, termination of corticosteroid treatment usually results in a decrease in IOP to normal levels within a few days.[60]

A growing body of evidence shows a rise in IOP after long-term anti-VEGF therapy. Patients without any previous history of glaucoma or ocular hypertension developed sustained elevation of IOP after receiving intravitreal injections of bevacizumab, ranibizumab, or pegaptanib.[61-65] The number of intravitreal injections is associated with an increased risk for IOP elevation (>5 mmHg) on ≥2 consecutive visits in patients with age-related macular degeneration (AMD) receiving bevacizumab or ranibizumab.[66] Male gender and the length of interval

between injections have been identified as risk factors for IOP elevation. The prevalence of IOP elevation was significantly higher when the interval between injections was <8 weeks than ≥8 weeks.[67]

There is a need for a method to detect patients at risk for IOP rise from corticosteroids, as this could provide a useful guide in developing a management strategy for individual patients with DME. The topical dexamethasone provocative test before IVTA injection showed low sensitivity but high specificity and positive predictive value, and may be useful to predict a steroid response after IVTA. Dexamethasone test responders demonstrated high IOP increases after IVTA, and the IOP increase after the test correlated with the IOP increase after IVTA.[68] A similar topical Prednisolone acetate trial (PAT) found that patients who did not have a short-term IOP rise following the PAT had a lower risk of severe IOP spikes after IVTA compared with those patients receiving IVTA but not having undergone a PAT.[69]

Further long-term advantages may be associated with the use of the ILUVIEN® FAc implant. Low doses of FAc have been found to be neuroprotective in animal models of retinal degeneration.[70,71] These findings may have a therapeutic role in human photoreceptor cell degenerations, and ILUVIEN® is currently being studied in clinical trials with respect to other chronic eye diseases.

The value of combination therapies (both FAc with other medications as well as medications with photocoagulation laser treatments) is yet to be determined. Phase II trials are being conducted to compare the safety and efficacy of 0.2 and 0.5 µg/day of FAc with sham injection in patients with bilateral geographic atrophy secondary to dry AMD. A further trial has been designed to examine the safety and efficacy of FAc in patients with macular edema secondary to retinal vein occlusion (RVO).

Conclusion

In summary, intravitreal delivery of corticosteroid agents have shown efficacy in the treatment of DME but are associated with adverse effects including cataract progression and rises in IOP, leading to research into intravitreal implants. Sustained release of low doses of steroid may be more effective than frequent bolus injections. A number of platforms for sustained drug delivery to the retina have been evaluated. The ILUVIEN® FAc implant is the first pharmacological therapy for DME that exerts a therapeutic effect for a prolonged period in a large proportion of patients. This implant will provide a novel treatment option for patients with chronic DME as well as give insight into the pathogenesis of the disease.

The FAME trials' entry requirement of at least one prior macular laser treatment made the FAME population unique and allowed for the signal to be reproducibly detected in two Phase III trials and showed that a continuous, long-term, low-dose, steroid delivery implant could provide a significant additional benefit to DME patients with chronic disease.

The FAc intravitreal implant provides significant, long-lasting improvements in VA for patients with chronic DME and has a manageable safety profile. From the surgeon's perspective, there is a short learning curve to be overcome for administering the device, but from the patients' perspective the procedure seems to be well tolerated. The release rate of steroid inside the eye is important and can be adjusted in a manner to significantly reduce some side effects while sustaining benefit. The technology of the implant allows for up to 36 months of drug delivery from a single micro implant. Considering the difficulties clinicians face when working in a resource-capped healthcare system in providing monthly VEGF antagonist treatment to a large number of patients, a single implant that lasts for up to three years becomes extremely attractive. Moreover, this innovation is likely to stimulate research initiatives to use the newly validated platform to optimise delivery of other drugs to the retina. ■

1. Aiello LM, Perspectives on diabetic retinopathy, *Am J Ophthalmol,* 2003;136:122–35.
2. CDCP, From the centers for disease control and prevention. blindness caused by diabetes--massachusetts, 1987–1994, *JAMA*, 1996;276:1865–6.
3. Klein R, Knudtson MD, Lee KE, et al., The wisconsin epidemiologic study of diabetic retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes, *Ophthalmology*, 2009;116:497–503.
4. Yau JW, Rogers SL, Kawasaki R, et al., Global prevalence and major risk factors of diabetic retinopathy, *Diabetes Care*, 2012;35:556–64.
5. Ehrlich R, Harris A, Ciulla TA, et al., Diabetic macular oedema: physical, physiological and molecular factors contribute to this pathological process, *Acta Ophthalmol,* 2010;88:279–91.
6. Brucklacher RM, Patel KM, VanGuilder HD, et al., Whole genome assessment of the retinal response to diabetes reveals a progressive neurovascular inflammatory response, *BMC Med Genomics,* 2008;1:26.
7. Kelly BD, Hackett SF, Hirota K, et al., Cell type-specific regulation of angiogenic growth factor gene expression and induction of angiogenesis in nonischemic tissue by a constitutively active form of hypoxia-inducible factor 1, *Circ Res,* 2003;93:1074–81.
8. Kern TS, Contributions of inflammatory processes to the development of the early stages of diabetic retinopathy, *Exp Diabetes Res,* 2007;2007:95–103.
9. Nguyen QD, Shah SM, Van Anden E, et al., Supplemental oxygen improves diabetic macular edema: a pilot study, *Invest Ophthalmol Vis Sci,* 2004;45:617–24.
10. Ozaki H, Yu AY, Della N, et al., Hypoxia inducible factor-1alpha is increased in ischemic retina: temporal and spatial correlation with VEGF expression, *Invest Ophthalmol Vis Sci,* 1999;40:182–9.
11. Zeng HY, Green WR, Tso MO, Microglial activation in human diabetic retinopathy, *Arch Ophthalmol,* 2008;126:227–32.
12. Shams N, Ianchulev T, Role of vascular endothelial growth factor in ocular angiogenesis, *Ophthalmol Clin North Am,* 2006;19:335–44.
13. Miyamoto N, de Kozak Y, Jeanny JC, et al., Placental growth factor-1 and epithelial haemato-retinal barrier breakdown: potential implication in the pathogenesis of diabetic retinopathy, *Diabetologia*, 2007;50:461–70.
14. Cai W, Rook SL, Jiang ZY, et al., Mechanisms of hepatocyte growth factor-induced retinal endothelial cell migration and growth, *Invest Ophthalmol Vis Sci,* 2000;41:1885–93.
15. ETDR, Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group, *Arch Ophthalmol,* 1985;103:1796–806.
16. Klein R, Klein BE, Moss SE, et al., The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema, *Ophthalmology*, 1984;91:1464–74.
17. DRCR, A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema, *Ophthalmology*, 2008;115:1447–9, 9 e1–10.
18. Elman MJ, Aiello LP, Beck RW, et al., Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema, *Ophthalmology*, 2010;117:1064–77 e35.
19. Massin P, Bandello F, Garweg JG, et al., Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study, *Diabetes Care,* 2010;33:2399–405.
20. Nguyen QD, Shah SM, Heier JS, et al., Primary End Point (Six Months) Results of the Ranibizumab for Edema of the mAcula in diabetes (READ-2) study, *Ophthalmology*, 2009;116:2175–81 e1.
21. 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;118:615–25.
22. 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;118:609–14.
23. Boras I, Lazic R, Gabric N, et al., Anti-VEGF in treatment of diabetic macular edema, *Coll Antropol,* 2011;35 Suppl 2:15–8.
24. 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*, 2011;117:1078–86 e2.
25. 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.
26. Sultan MB, Zhou D, Loftus J, et al., A phase 2/3, multicenter, randomized, double-masked, 2-year trial of pegaptanib sodium for the treatment of diabetic macular edema, *Ophthalmology*, 2011;118:1107–18.
27. Kompella UB, Bandi N, Ayalasomayajula SP, Subconjunctival nano- and microparticles sustain retinal delivery of budesonide, a corticosteroid capable of inhibiting VEGF expression, *Invest Ophthalmol Vis Sci,* 2003;44:1192–201.
28. Tamura H, Miyamoto K, Kiryu J, et al., Intravitreal injection of corticosteroid attenuates leukostasis and vascular leakage in experimental diabetic retina, *Invest Ophthalmol Vis Sci,* 2005;46:1440–4.
29. Wang K, Wang Y, Gao L, et al., Dexamethasone inhibits leukocyte accumulation and vascular permeability in retina of streptozotocin-induced diabetic rats via reducing vascular endothelial growth factor and intercellular adhesion molecule-1 expression, *Biol Pharm Bull,* 2008;31:1541–6.
30. Schwartz SG, Flynn HW, Jr., Scott IU, Pharmacotherapy for diabetic retinopathy, *Expert Opin Pharmacother,* 2009;10:1123–31.
31. Jager RD, Aiello LP, Patel SC, et al., Risks of intravitreous injection: a comprehensive review, *Retina*, 2004;24:676–98.
32. Lam DS, Chan CK, Mohamed S, et al., A prospective randomised trial of different doses of intravitreal triamcinolone for diabetic macular oedema, *Br J Ophthalmol,* 2007;91:199–203.
33. Kim JE, Pollack JS, Miller DG, et al., ISIS-DME: a prospective, randomized, dose-escalation intravitreal steroid injection study for refractory diabetic macular edema, *Retina*, 2008;28:735–40.
34. Gillies MC, Simpson JM, Gaston C, et al., Five-year results of a randomized trial with open-label extension of triamcinolone acetonide for refractory diabetic macular edema, *Ophthalmology*, 2009;116:2182–7.
35. Beck RW, Edwards AR, Aiello LP, et al., Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema, *Arch Ophthalmol,* 2009;127:245–51.
36. Chew E, Strauber S, Beck R, et al., Randomized trial of

peribulbar triamcinolone acetonide with and without focal photocoagulation for mild diabetic macular edema: a pilot study, *Ophthalmology*, 2007;114:1190–6.
37. Lee SS, Robinson MR, Novel drug delivery systems for retinal diseases. A review, *Ophthalmic Res*, 2009;41:124–35.
38. Kane FE, Burdan J, Cutino A, et al., Iluvien: a new sustained delivery technology for posterior eye disease, *Expert Opin Drug Deliv,* 2008;5:1039–46.
39. Diabetic Retinopathy Clinical Research Network, A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema, *Ophthalmology*, 2008;115:1447–9, 1449 e1–10,
40. Kuppermann BD, Blumenkranz MS, Haller JA, et al., Randomized controlled study of an intravitreous dexamethasone drug delivery system in patients with persistent macular edema, *Arch Ophthalmol,* 2007;125:309–17.
41. Haller JA, Kuppermann BD, Blumenkranz MS, et al., Randomized controlled trial of an intravitreous dexamethasone drug delivery system in patients with diabetic macular edema, *Arch Ophthalmol,* 2010;128:289–96.
42. Ayalasomayajula SP, Ashton P, Kompella UB, Fluocinolone inhibits VEGF expression via glucocorticoid receptor in human retinal pigment epithelial (ARPE-19) cells and TNF-alpha-induced angiogenesis in chick chorioallantoic membrane (CAM), *J Ocul Pharmacol Ther,* 2009;25:97–103.
43. Kane FE, Green, K.E., Weissman, A, Comparison of In Vitro Receptor Binding of Glucocorticoids. In poster session 106 (retinal Therapeutics) of Association of Research in Vision and Ophthalmology Annual Meeting, Poster B215, Fort Lauderdale, Florida, 6 May 2007, 2007.
44. Pearson PA, Comstock TL, Ip M, et al., Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial, *Ophthalmology*, 2011;118:1580–7.
45. Callanan DG, Jaffe GJ, Martin DF, et al., Treatment of posterior uveitis with a fluocinolone acetonide implant: three-year clinical trial results, *Arch Ophthalmol,* 2008;126:1191–201.
46. Jaffe GJ, Martin D, Callanan D, et al., Fluocinolone acetonide implant (Retisert) for noninfectious posterior uveitis: thirty-four-week results of a multicenter randomized clinical study, *Ophthalmology*, 2006;113:1020–7.
47. B&L, Fluocinolone acetonide ophthalmic--Bausch & Lomb: fluocinolone acetonide envision TD implant, *Drugs R D*, 2005;6:116–9.
48. Pearson P, Baker CW, Eliott D, et al., Fluocinolone acetonide intravitreal implant in patients with diabetic macular edema: 12 month results, *Invest. Ophthalmol. Vis. Sci.,* 2003;44:4288.
49. Pearson P, Levy B, Comstock T, et al., Fluocinolone acetonide intravitreal implant to treat diabetic macular edema: 3-year results of a multi-center clinical trial, *Invest. Ophthalmol. Vis. Sci.*, 2006;47:5442.
50. Pearson P, Levy B, Fluocinolone acetonide implant study group, fluocinolone acetonide intravitreal implant to treat diabetic macular edema: 2-year results of a multi-center clinical trial, *Invest. Ophthalmol. Vis. Sci.*, 2005;46:4673.
51. Campochiaro PA, Nguyen, Q., Hafiz, G., et al, Aqueous levels of fluocinolone acetonide (FAc) after administration of FAc inserts or FAc implants 2010.
52. 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;.
53. Campochiaro PA, Hafiz G, Shah SM, et al., Sustained ocular delivery of fluocinolone acetonide by an intravitreal insert, *Ophthalmology*, 2010;117:1393–9 e3.
54. Campochiaro PA, Brown DM, Pearson A, et al., Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema, *Ophthalmology*, 2011;118:626–35 e2.
55. Gillies MC, McAllister IL, Zhu M, et al., Intravitreal triamcinolone prior to laser treatment of diabetic macular edema: 24-month results of a randomized controlled trial, *Ophthalmology*, 2011;118:866–72.
56. Armaly MF, Effect of corticosteroids on intraocular pressure and fluid dynamics I:the effect of dexamethasone in the normal eye, *Arch Ophthalmol*, 1963;70:428–291.
57. Jones RI, Rhee DJ, Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature, *Curr Opin Ophthalmol,* 2006;17:163–7.
58. Kersey JP, Broadway DC, Corticosteroid-induced glaucoma: a review of the literature, *Eye (Lond),* 2006;20:407–16.
59. Zhang X, Clark AF, Yorio T, FK 506-binding protein 51 regulates nuclear transport of the glucocorticoid receptor beta and glucocorticoid responsiveness., *Invest Ophthalmol Vis Sci,* 2008;49:1037–47.
60. Weinreb RN, Polansky JR, Kramer SG, Acute effects of dexamethasone on intraocular pressure in glaucoma, *Invest Ophthalmol Vis Sci,* 1985;26:170–5.
61. Adelman RA, Zheng Q, Mayer HR, Persistent ocular hypertension following intravitreal bevacizumab and ranibizumab injections, *J Ocul Pharmacol Ther,* 2010;26:105–10.
62. Bakri SJ, McCannel CA, Edwards AO, et al., Persistent ocular hypertension following intravitreal ranibizumab, *Graefes Arch Clin Exp Ophthalmol,* 2008;246:955–8.
63. Choi DY, Ortube MC, McCannel CA, et al., Sustained elevated intraocular pressures after intravitreal injection of bevacizumab, ranibizumab, and pegaptanib, *Retina*, 2011;31:1028–35.
64. Good TJ, Kimura AE, Mandava N, et al., Sustained elevation of intraocular pressure after intravitreal injections of anti-VEGF agents, *Br J Ophthalmol,* 2011;95:1111–4.
65. Kahook MY, Kimura AE, Wong LJ, et al., Sustained elevation in intraocular pressure associated with intravitreal bevacizumab injections, *Ophthalmic Surg Lasers Imaging,* 2009;40:293–5.
66. Hoang QV, Mendonca LS, Della Torre KE, et al., Effect on intraocular pressure in patients receiving unilateral intravitreal anti-vascular endothelial growth factor injections, *Ophthalmology*, 2012;119:321–6.
67. Mathalone N, Arodi-Golan A, Sar S, et al., Sustained elevation of intraocular pressure after intravitreal injections of bevacizumab in eyes with neovascular age-related macular degeneration, *Graefes Arch Clin Exp Ophthalmol,* 2012;.
68. Breusegem C, Vandewalle E, Van Calster J, et al., Predictive value of a topical dexamethasone provocative test before intravitreal triamcinolone acetonide injection, *Invest Ophthalmol Vis Sci,* 2009;50:573–6.
69. Hollands H, Seif G, Hollands S, et al., A trial of topical prednisolone acetate before intravitreal triamcinolone acetonide decreases intraocular pressure spikes, *Can J Ophthalmol,* 2010;45:484–8.
70. Glybina IV, Kennedy A, Ashton P, et al., Photoreceptor neuroprotection in RCS rats via low-dose intravitreal sustained-delivery of fluocinolone acetonide, *Invest Ophthalmol Vis Sci,* 2009;50:4847–57.
71. Glybina IV, Kennedy A, Ashton P, et al., Intravitreous delivery of the corticosteroid fluocinolone acetonide attenuates retinal degeneration in S334ter-4 rats, *Invest Ophthalmol Vis Sci,* 2010;51:4243–52.