

Early Experience With Iluvien for the Treatment of Chronic DME

Fluocinolone acetonide implants are a valuable addition to the limited treatment options available for these patients.

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Macular edema is a frequent manifestation of diabetic retinopathy and a significant cause of impaired vision in individuals with diabetes. In Europe, nearly 5.4% of patients with diabetes are estimated to experience visual impairment due to diabetic macular edema (DME).¹

DME is a pathologic condition characterized by the breakdown of the blood-retina barrier and a consequent increase in vascular permeability. New insights into retinal physiology suggest that the retinal dysfunction associated with DME is characterized by a multifactorial pathophysiology (Figure 1).² Additionally, it is known that the up-regulation of inflammatory factors, including VEGF^{3,4} and intercellular adhesion molecule-1,⁵ or the down-regulation of antiinflammatory factors such as pigment epithelium-derived factor⁶ can lead to the breakdown of the blood-retina barrier in DME. Therapeutic strategies for DME target 1 or more of the associated inflammatory pathways.

CURRENT TREATMENT OPTIONS

Laser photocoagulation has been the standard of care for DME for many years; it reduces the incidence of visual loss by up to 50%.⁷ More recently, intravitreal injections of anti-VEGF agents such as ranibizumab (Lucentis, Genentech) and bevacizumab (Avastin, Genentech) have become commonplace. In addition, corticosteroids have recently found use in DME treatment (Table 1). Ranibizumab is an anti-VEGF antibody that is approved for the treatment of DME in many countries. It has been shown that ranibizumab is effective in reducing central macular thickness (CMT) and improving BCVA in DME over a 12- to 36-month follow-up period.⁸ The recent approval of ranibizumab for DME by the US Food and

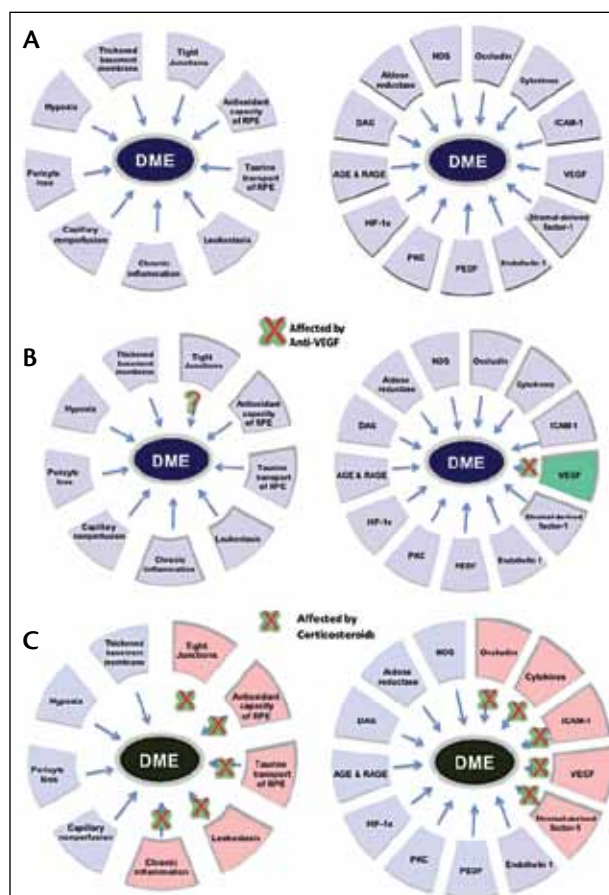


Figure 1. Multifactorial pathophysiology of DME and possible targets for therapy, showing (A) the different anatomic, physiologic, and biochemical pathways involved in DME, (B) the pathways and processes affected by anti-VEGF agents, and (C) the pathways affected by corticosteroids. Adapted from: www.atpo.org/documents/handouts/DME.pdf.

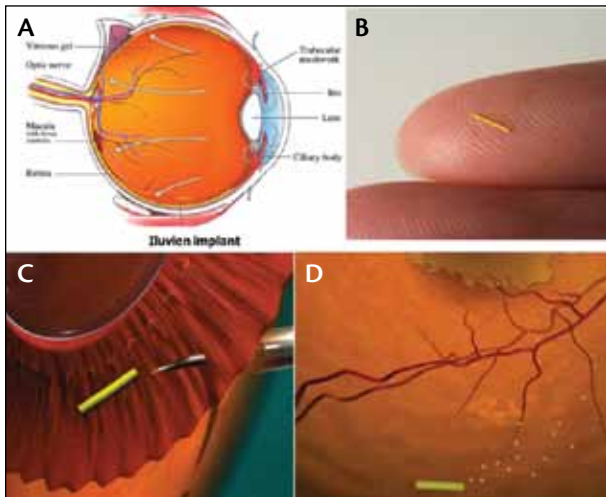


Figure 2. (A) The location and (B) size of the Iluvien implant. (C) The site of injection and the interior view of the delivery of the Iluvien implant via the pars plana. (D) The location of the Iluvien implant in inferior vitreous.

Drug Administration has highlighted systemic safety concerns that prompted the agency to approve a lower dose (0.3 mg); the product carries a black box warning on its US label.

Corticosteroids suppress multiple pathways of inflammation and reduce damage to the blood-retina barrier,⁹ and they provide an excellent therapeutic strategy for DME (Figure 1).

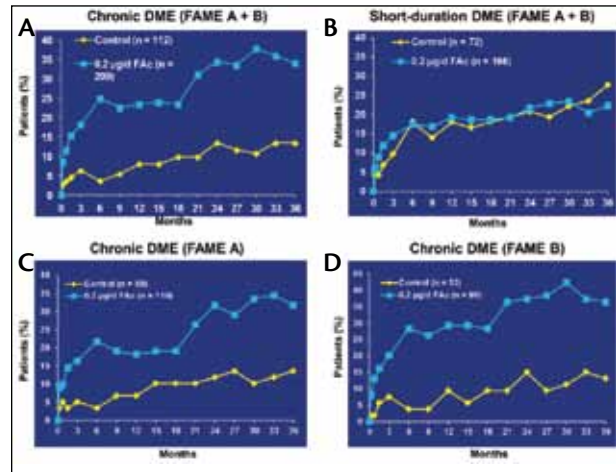


Figure 3. Summary of the FAME study results. Percentage of patients with ≥ 15 -letter improvement over baseline assessed using the integrated dataset of the FAME A and FAME B studies is shown for patients with (A) chronic DME (duration ≥ 3 years) and (B) short-duration DME. Percentage of patients with ≥ 15 -letter improvement over baseline assessed independently for FAME A (C) and FAME B (D) studies is shown.

Iluvien

Iluvien (Alimera Sciences Inc.) is an injectable intra-vitreous microimplant providing sustained-release, low-dose fluocinolone acetonide. It is composed of an inert, nonbiodegradable, polyimide material that is often used in the manufacturing of certain intraocular lenses. The

TABLE 1. COMPARATIVE ANALYSIS OF CORTICOSTEROIDS*

Compound (Brand Name)	Intravitreal Dose and Duration	Estimated Daily Dose	Total dose	Procedure	Duration of Action
Triamcinolone acetonide (Kenalog)	4 mg, 3 months	44.4 µg/day	4 mg	Injectable	~3 months
Fluocinolone acetonide (Retisert)	0.59 mg, 30 months	0.6 µg/day initially, 0.3-0.4 µg/day after 1 month	500 µg	Incision and suture	2.5 years
Dexamethasone (Ozurdex)	700 µg, 3-6 months	11.7 µg/day	750 µg	Injectable	~4 months
Fluocinolone acetonide (Iluvien)	0.5 µg, 18-24 months or 0.2 µg, 24-30 months	0.5 or 0.2 µg/day	190 µg	Injectable	3 years

*Adapted from Kane et al¹² and Campochiaro et al¹³

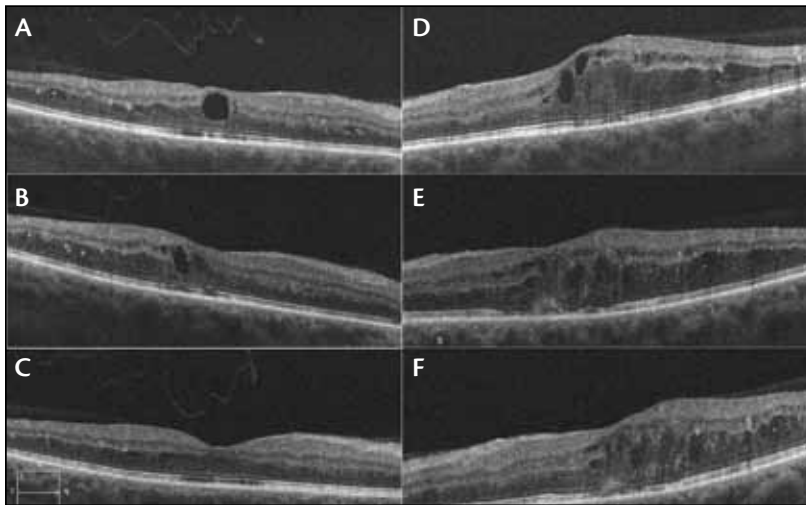


Figure 4. First patient treated with Iluvien. (A) Right eye (OD) before injection. BCVA 1.0 logMAR (0.1); CMT 389 μ m. (B) OD 7 days after injection. BCVA 0.9 logMAR (0.125); CMT 326 μ m. (C) OD 8 weeks after injection (post cataract surgery). BCVA 0.1 logMAR (0.8); CMT 316 μ m. (D) Left eye (OS) before injection. BCVA 1.3 logMAR (0.05); CMT 502 μ m. (E) OS 7 days after injection. BCVA 1.0 logMAR (0.1); CMT 441 μ m. (F) OS 8 weeks after injection (post cataract surgery). BCVA 0.2 logMAR (0.63); CMT 410 μ m.

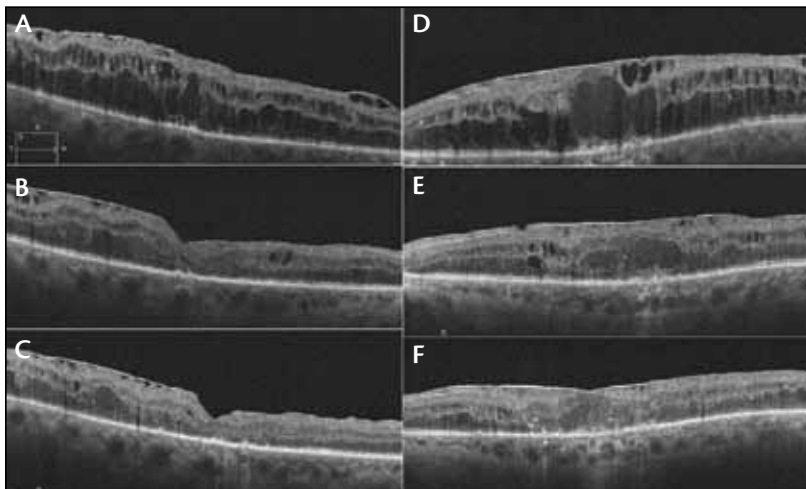


Figure 5. Second patient treated with Iluvien. (A) OD before injection. BCVA 1.0 logMAR (0.1); CMT 536 μ m. (B) OD 1 week after injection. BCVA 0.5 logMAR (0.32); CMT 352 μ m. (C) OD 4 weeks after injection. BCVA 0.5 logMAR (0.32); CMT 274 μ m. (D) OS before injection. BCVA 1.0 logMAR (0.1); CMT 677 μ m. (E) OS 1 week after injection. BCVA 0.8 logMAR (0.16); CMT 521 μ m. (F) OS 4 weeks after injection. BCVA 0.6 logMAR (0.25); CMT 387 μ m.

implant is a cylindrical tube (3.5 mm in length, 0.37 mm in diameter) that holds 190 μ g of fluocinolone acetonide (Figure 2). The implant is injected into the vitreous using a 25-gauge proprietary inserter, which creates a self-sealing wound. Iluvien is available in a 0.2- μ g dose,

which shows sustained drug release over a 36-month period.¹⁰

THE FAME STUDY

Study Design

The efficacy and safety of Iluvien has been examined in controlled trials, called the FAME studies. These 2 clinical trials, FAME A and FAME B, were randomized, double-masked, sham injection-controlled, parallel group, multicenter trials performed under the same protocol.

Patients with persistent DME were eligible for the FAME studies if they had center point retinal thickness of 250 μ m or greater despite at least 1 prior macular laser treatment and a BCVA Early Treatment Diabetic Retinopathy Study letter score between 19 and 68 (20/50 to 20/400).¹¹ A total of 956 patients were randomized 2:2:1 to receive 0.2 μ g/day fluocinolone acetonide, 0.5 μ g/day fluocinolone acetonide, or sham injection. Patients were allowed to receive rescue laser therapy any time after week 6 at the discretion of the observing physician and retreatment after month 12 if they experienced a loss of 5 or more letters of BCVA or had a 50 μ m or greater increase in foveal thickness compared with their best status during the previous 12 months. The primary endpoint, assessed at 24 months, was the percentage of patients with improvement from baseline in BCVA of 15 letters or more. Follow-up continued after the 2-year primary endpoint, and the 3-year results have been published.¹¹

Study Results

At month 36, the percentage of patients demonstrating an improvement of 15 letters or more was 28.7%

in the low-dose group and 27.8% in the high-dose group, compared with 18.9% ($P = .018$) in the sham group. At month 36, almost all phakic patients in the fluocinolone acetonide implant groups developed cataract, but their visual benefit after cataract surgery was

similar to that in pseudophakic patients (see below). The incidence of incisional glaucoma surgery at month 36 was 4.8% in the low-dose group, 8.1% in the high-dose group, and 0.5% in the sham group. In patients who underwent surgery to lower intraocular pressure, mean visual acuity outcomes were not compromised.

The median duration of DME at baseline was 3 years. Therefore, based on a preplanned subgroup analysis, outcomes were assessed in patients having DME for less than 3 years and for 3 years or more (chronic DME) at baseline. In the integrated data set of the FAME studies, the percentage of chronic DME patients who gained 15 letters of BCVA or more from baseline at month 36 was 13.4% in the sham group, 34% in the low-dose implant group ($P < .001$), and 28.8% in the high-dose implant group ($P = .002$; Figure 3A). The percentage of patients with DME of less than 3 years' duration who gained 15 letters or more was 27.8% in the sham group, 22.3% in the low-dose group, and 26.4% in the high-dose group; the differences were not significantly different between groups (Figure 3B).

Based on the evidence reported in the FAME studies, particularly in patients with chronic DME, Iluvien has been approved in the European Union for the treatment of visual impairment due to chronic macular edema considered insufficiently responsive to available therapies.

CLINICAL EXPERIENCE

Our early anecdotal experience with Iluvien has supported the results of the FAME studies.

Case No. 1

A 51-year-old diabetic patient with macular edema who was unresponsive to repeated intravitreal anti-VEGF injections received Iluvien. At 5 and 6 weeks after the Iluvien application, uneventful cataract surgery was performed in both eyes. Eight weeks after the Iluvien application, the edema has been reduced considerably, with a significant visual gain in both eyes (Figure 4).

Case No. 2

A 68-year-old pseudophakic patient with an epiretinal membrane and macular edema, which was unresponsive to repeated anti-VEGF and steroid injections, showed an impressive anatomic improvement after Iluvien injection in both eyes. The patient gained 2 lines of BCVA in both eyes over a 4-week period after the injection of Iluvien. He tolerated the medication well and did not develop an increase in intraocular pressure (Figure 5).

No adverse event has been noted in either of our 2 patients treated with Iluvien. Iluvien has received marketing authorization approval in Austria, France, Germany,

Portugal, Spain, and the United Kingdom and is going through the national phase of the approval process in Italy. The manufacturer is currently seeking regulatory approval in the United States.

CONCLUSIONS AND FUTURE DIRECTIONS

The relative benefit compared with the sham group was markedly better for those patients with chronic DME (duration ≥ 3 years). The results suggest that patients with persistent DME who do not respond well to currently available treatments respond well to the administration of a fluocinolone acetonide implant.

In patients with short-duration DME, treatment may be initiated with laser therapy and/or anti-VEGF injections. In vitrectomized eyes with persistent DME despite focal/grid laser or eyes with chronic DME that have a functioning glaucoma filter, the addition of fluocinolone acetonide implants may be considered very early on.¹¹ One of our patients (case No. 2) was vitrectomized, and the application of the implant was performed uneventfully. Overall, fluocinolone acetonide implants provide a valuable addition to the limited treatment options available for patients with chronic DME. ■

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