

Diabetes & its Complications

Treatment of Diabetic Macular Edema with ILUVIEN (Fluocinolone Acetonide 0.19mg): Pharmacokinetics and Lipophilicity for the Primary Care Provider

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ABSTRACT

Diabetes mellitus is an epidemic worldwide. Primary care providers, including advanced practice registered nurses, can play a vital role in both the treatment of the disease and prevention of complications, particularly diabetic macular edema. A working understanding of the disease process and early referral is of exceptional importance, as are long term treatment options patients may receive from their ophthalmologist. ILUVIEN® (fluocinolone acetonide (FAc) intravitreal implant) 0.19 mg is an implant injected into the eye (vitreous) and used for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant increase in intraocular pressure. The implant of ILUVIEN, a corticosteroid, provides a continuous microdose of FAc for up to 36 months. One must understand the pharmacokinetics of a drug as not all corticosteroids have the same lipophilicity, water solubility and tissue penetration as well as its lipophilic nature. The lipophilicity of FAc allows for the continuous use of a microdose that is readily absorbed into the retina, which explains why the FAc continuous microdose can stabilize or improve vision for many patients, while reducing retinal edema. It is important for the primary care provider to appreciate the features of the drug and understand the implications of diabetic macular edema. Assertive, collaborative treatment is imperative for this patient population to maintain vision through their lifetime.

Keywords

Diabetic macular edema, ILUVIEN, Fluocinolone acetonide, Primary care.

Diabetes as a National Epidemic

It has been well documented that Type 2 diabetes mellitus (DM2) is a national epidemic in the United States. The Centers for Disease Control and Prevention estimated that in 2012, over 29 million people were diagnosed with DM2, and 1 in 4 people were undiagnosed. These statistics were even grimmer for those considered pre-diabetic: 86 million were prediabetic with 9 of 10 being unaware. Given these numbers, it is no surprise that primary care providers (PCPs) would see more patients with a myriad of complications, including those affecting vision. Diabetic macular

edema (DME) is one of them; improved appreciation of this disease process and its treatments could enable PCPs to make a timelier referral, thereby positively affecting the patient's vision over time, which when lost, may never be regained.

Diabetic Macular Edema

According to Bandello et al. DME, defined as "retinal thickening involving or approaching the center of the macula, represents the most common cause of vision loss in patients affected by diabetes mellitus." DME is a multi-factorial disease process which includes multiple inflammatory cytokines and biochemical factors driven by local and systemic disease processes (Figure 1). For the PCP, management of the systemic disease is an important part of preventing ocular complications, but early referrals to ophthalmologists and retina specialists are equally important.

Understanding treatment options is critical, as some have systemic affect.

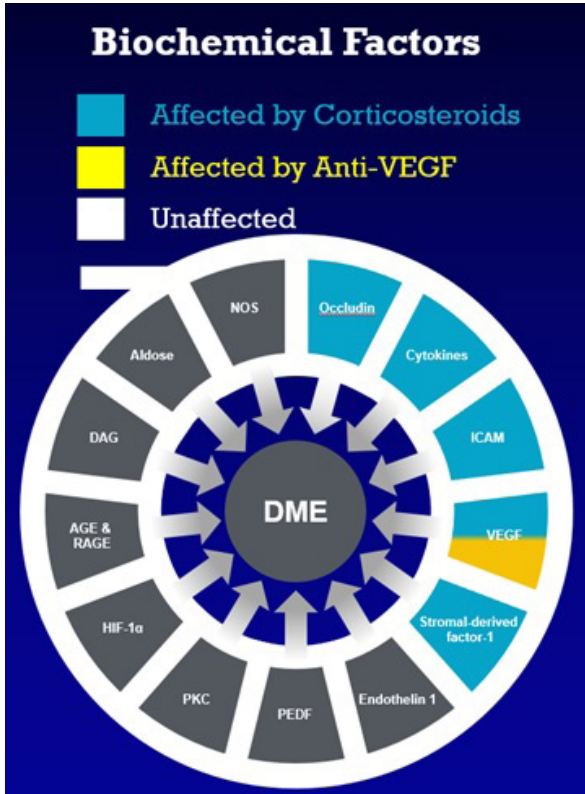


Figure 1: Biochemical Factors and the Treatments that affect them in DME.

ILUVIEN (fluocinolone acetonide 0.19mg implant) as a Foundational Therapy for DME

ILUVIEN has been available in Europe since 2014 and in the US since 2015 (Figure 2). The US label indicates that it is for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. One trial of any ocular steroid, topical or intravitreal is sufficient to identify IOP hyper-responders. In the FAME study, ILUVIEN met the primary endpoint of proportion of patients with ≥ 15 -letter improvement in BCVA from baseline at month 24 with sustained improvements through 36 months. The secondary endpoint of reduced retinal thickness was also met through 36 months. Class effect of cataract development and intraocular pressure elevation were the most common adverse events. Similar results were also seen in the USER study (Figure 3). Reduction in treatment frequency was also noted versus other options such as laser or anti angiogenic ocular injections

Pharmacokinetics and Lipophilicity

ILUVIEN is the novel treatment option as it combines a well-known steroid with an innovative technology. The fluocinolone acetonide 0.19mg implant contains a lipophilic molecule which is encased in a semi-permeable, polyimide shell approximately 3.5 mm long by 0.37 mm in diameter. It is implanted through as 25G needle into the eye and can last up to 36 months. This technology

allows ILUVIEN to obtain near zero order pharmacokinetics and treat the retina with a continuous microdose of steroid. The continuous microdosing in turn can result in decreased frequency of treatment over time as demonstrated in Figure 3.

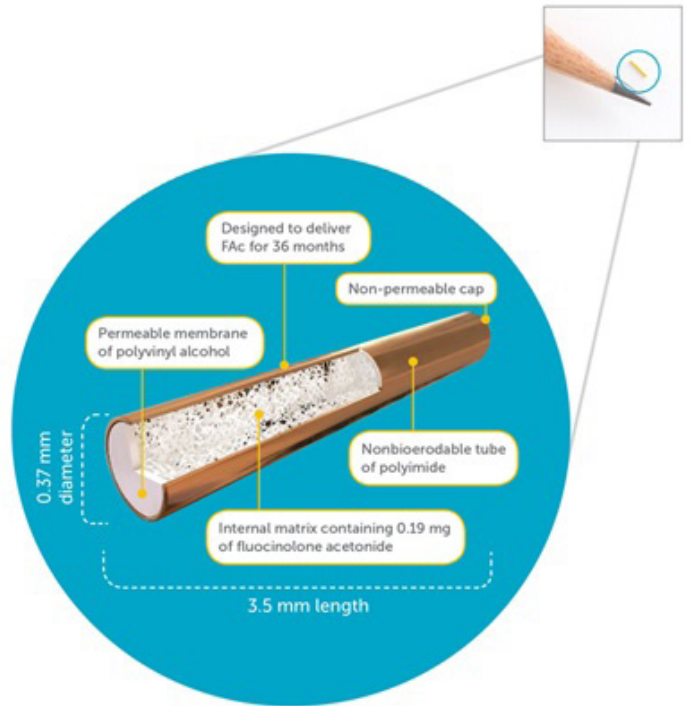


Figure 2: The ILUVIEN implant.

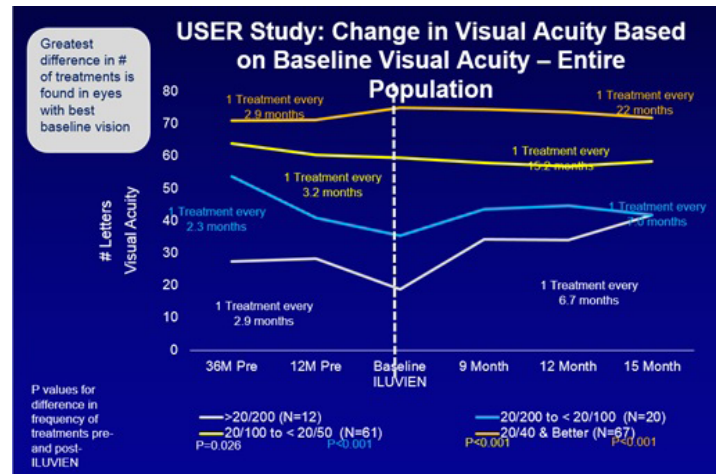


Figure 3: USER Study Visual Outcomes and Reduction in Treatment Frequency.

Implications for the PCP

Vision is of critical importance to the PCP as it affects multiple areas of patients' lives including:

- Visual-Motor Integration - Eye-hand/foot/body coordination.
- Visual-Auditory Integration - Associate what is seen and heard.
- Visual Memory - Remember and recall information that is seen.
- Visual Closure - Complete a visual picture based on seeing only some of the parts.

- Spatial Relationships - "Where I am" in relation to objects and space/where objects are in relation to one another.
- Figure-Ground Discrimination - Discern form and object from background. (Brainline.org).

The PCP plays an integral part in vision preservation. Systemic factors such as hypertension, glycemic control, renal impairment and lipid control can have a negative impact on long term vision, therefore appropriate management is important for vision protection. As previously discussed, prompt referral and long-term collaboration with local ophthalmologists and retina specialists is an important part in the continuum of care for the diabetic patient. Appreciation of the pathophysiology and treatment of DME, such as with ILUVIEN, can help enhance PCP competence in the care of the diabetic patient. Consultation between providers can help prevent untoward side effects of intravitreal and systemic medications due to a breached blood retinal barrier [1-7].

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