

Christopher Wolfe, OD, FAAO, Dipl. ABO



Epiretinal Membrane (ERM) and Vitreomacular Traction (VMT)

Epiretinal membrane (macular pucker, cellophane maculopathy, premacular fibrosis) consists of a layer of avascular, fibrocellular tissue that can develop on the surface of the retina at the inner limiting membrane [1].

Symptoms

Often asymptomatic but can cause a reduction in BCVA and distortion of vision.

Signs

ERMs can appear as a **shiny film** over the surface of the retina, often the macula. As they thicken they can appear as **gray or white fibrous tissue**. As the membrane causes traction on the underlying retina, we may see **retinal folds**, **changing of the retinal vessels** (tortuosity or straightening). Occasionally this traction can lead to **macular edema**, **macular holes** or **retinal detachments** [2].

Pathophysiology

The source of the cells producing these membranes may come from:

1. Glial cells, which are primarily fibrous astrocytes, **liberated from the inner layers of the neurosensory retina by small breaks in the internal limiting membrane** (ILM) that can occur after retinal tears or a posterior vitreous detachments [3]
2. Retinal pigment epithelial cells from retinal tears or PVD
3. Macrophages from intraocular inflammation
4. **Fibrocytes and collagen cells from remnants of the vitreous after a PVD**

PVD

Association

75-93% of all eyes with an ERM will also have a PVD. ERM formation without a PVD places patients at risk for vitreomacular traction (VMT) [17].

Demographics

The underlying causative disease impacts the frequency that an ERM will be seen.

- Idiopathic membranes may exist in approximately 7-34% of the population [4]
- After intraocular surgery 3-8.5% of eyes may have an ERM [5]
- ERMs appear to impact women slightly more frequently than men (3:2) [6]
- Incidence increases with increasing age

Traditional Treatment and Management

The majority of ERMs will remain relatively stable and will not require treatment. Patients with areas of VMT that are 1500 μm or less, spontaneous release occurs in about 30-40% of eyes over 1-2 years (more on this below) [4].

Vitrectomy is indicated in patients where the benefits outweigh the risks with symptoms including:

Vitreomacular Update for the Primary Care OD

- Decrease in visual acuity (~20/50 or worse)
- Significant metamorphopsia
- Monocular diplopia
- Poor binocularity from any of the above

Vitreotomy surgery for ERM or VMT usually leads to improvement of the metamorphopsia and visual acuity in about 75% of patients and we can expect to regain at least 2 lines of visual acuity [4].

Macular Hole (MH)

Symptoms

Decreased visual acuity, scotoma, metamorphopsia

Signs

Visual acuity can be reduced 20/40-20/400 and can be classified based on ophthalmoscopic appearance and OCT appearance.

Ophthalmoscopic Grading Scale

- Stage 1 – loss of foveal depression with a yellow spot or ring
- Stage 2 – Full thickness hole overlying **pseudo-operculum**
- Stage 3 – Full thickness hole with **overlying operculum – NO PVD**
- Stage 4 – Full thickness hole with **overlying operculum – W/ PVD**

Optical Coherence Tomography Grading Scale [7]

- **Vitreomacular Adhesion (VMA)** – Vitreous base is adhered to the macula with a detachment of the vitreous surrounding the adhesion **without distortion of the sensory retina**
- **Vitreomacular Traction (VMT)** – Vitreous base is adhered to the macula with a detachment of the vitreous surrounding the adhesion **with** distortion of the sensory retina
- **Stage 1 hole** – Full thickness hole down to the level of the retinal pigmented epithelium (RPE) **with a closed cap of tissue above the hole** and no breaks in the cap
- **Stage 2 hole** – Full thickness hole down to the level of the RPE with **adhesion of the vitreous to the edge of the hole and a break in the cap**
- **Stage 3 hole** – Full thickness hole down to the level of the RPE with a **posterior vitreous detachment above the macula**
- **Stage 4 hole** – Full thickness hole down to the level of the RPE with a **complete posterior vitreous detachment**

Pathophysiology

Macular and holes can form from [6]:

1. Vitreous traction
2. Epiretinal membrane traction
3. Cystoid macular edema
4. Trauma

Traditional Treatment and Management

- Stage 1 holes - not typically treated due to the potential of spontaneous closure
- Stage 2-4 holes (< 1 year onset) - Pars Plana Vitrectomy with membrane peel and air-fluid exchange when VA is 20/40 or worse followed by 1-2 weeks of face down positioning [2] [6]

Literature Update

How effective is Jetrea® injection at resolving symptomatic VMA and MH and preventing the need for surgery [8]?

- (MIVI-Trust) 2 randomized multicenter, double-blind, clinical trials were completed to compare a single intravitreal injection of ocriplasmin (125 µg) with a placebo injection in patients with symptomatic VMA.
 - Primary end point - resolution of VMA at day 28
 - Secondary end points
 - Total PVD
 - Nonsurgical closure of a macular hole at day 28
 - Avoidance of vitrectomy
 - Change in best-corrected visual acuity
- RESULTS:
 - 652 eyes were treated:
 - Ocriplasmin: 464
 - Placebo: 188
 - **Vitreomacular adhesion resolved**
 - Ocriplasmin: 26.5%
 - Placebo: 10.1%
 - NNT: ~6
 - **Complete PVD**
 - Ocriplasmin: 13.4%
 - Placebo: 3.7%
 - NNT: ~10
 - **Nonsurgical closure of macular holes (<400 microns)**
 - Ocriplasmin: 40.6%
 - Placebo: 10.6%
 - NNT: 3.33
 - **Vitrectomy at 6 months**
 - Ocriplasmin: 17.7%
 - Placebo: 26.6%
 - NNT: ~11
 - **Improvement in VA at least 3 lines**
 - Ocriplasmin: 12.3%
 - Placebo: 6.4%
 - NNT: ~1

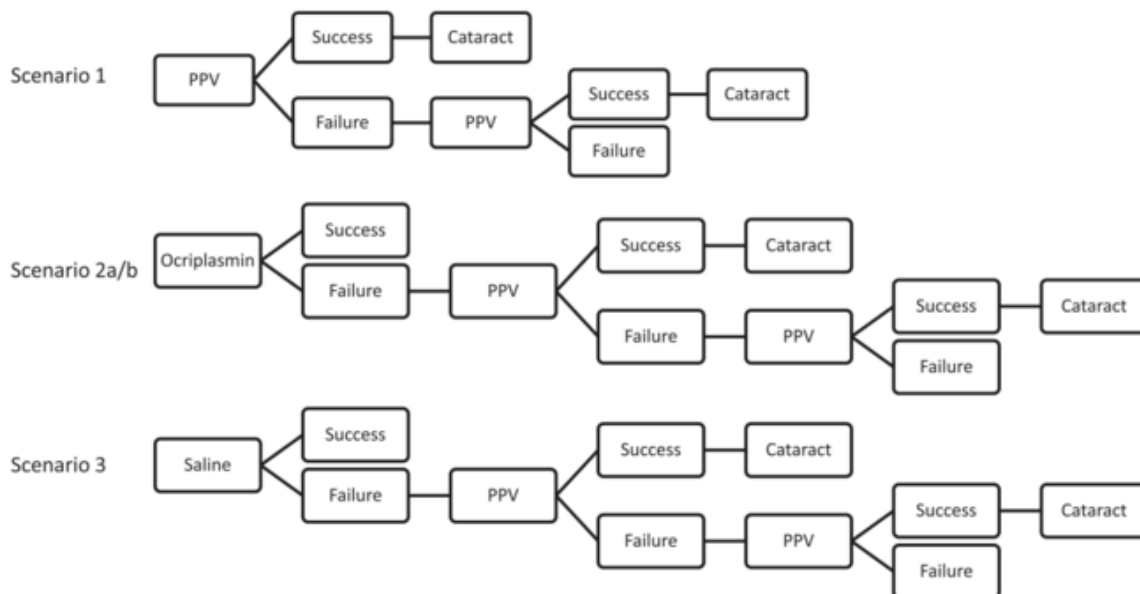
How many patients with MH can benefit from a Jetrea® injection? [7]

- A retrospective review of 135 patients with full-thickness MHs were evaluated to determine if ocriplasmin intravitreal injection was suitable based on the criteria described in the MIVI-TRUST reports.
- Vitreomacular adhesion was present in 19 eyes with MH (14.1%)
 - MH was 400 µm or less in only 9 eyes (6.7%)
 - Using the criteria of the MIVI-TRUST study exclusively, only these eyes were candidates for ocriplasmin injection.

- Based on the closure rate of 40%, as described in that study, only 2.7% of the patients in this review would have benefited from ocriplasmin injection.

How cost effective is Jetrea® compared to surgical treatment as the primary treatment for VMT and MH? [9] [10]

- Studies examined the cost effectiveness of treatments of VMA and MH by evaluating data from CMS and UK data against success rates of surgical and pharmaceutical treatments.
 - Success = BCVA improvement of ≥ 2.5 lines
- Pars plana vitrectomy with membrane peel and gas/fluid exchange remains the most cost effective treatment
- In order for ocriplasm to replace PPV the success rate would have to be:
- VMA: **Current:** 26.5%, **Cost Effective:** 71%
- MH: **Current:** 40.6%, **Cost Effective:** 87%



How necessary is face-down positioning in patients who undergo PPV with air-fluid exchange? [11]

- A retrospective review evaluated 68 patients over 3.5 years with full-thickness MH at any stage that were surgically repaired (1 surgeon) with:
 - PPV
 - Broad ILM peeling
 - ERM peeling (if needed)
 - Fluid-gas exchange
 - Reading position (45° down gaze) following surgery for 3-5 days
 - Followed for 1 month
- Results:
 - MH closure rate: 100%

- Mean pre-op VA: 20/95
- Mean post-op VA: 20/38
- 87% of patients achieved 20/50 or better
- A multicenter prospective study is underway to further evaluate these data [12].

Plaquenil Toxicity

Hydroxychloroquine (Plaquenil) is utilized systemically as prophylaxis for malaria and also to treat dermatological and rheumatological inflammatory conditions like systemic lupus erythematosus and rheumatoid arthritis [13].

Mechanism of Action

The exact mechanism of action of hydroxychloroquine is unknown, however, it is thought to have an impact on the following conditions by:

1. Malaria Treatment – hydrochloroquinine inhibits hemozoin biocrystallization, which leads to the **accumulation of cytotoxic heme** which builds up in the malaria parasite causing their deaths [14].
2. Anti-inflammatory – Hydroxychloroquine **increases lysosomal pH** (more basic) in antigen-presenting cells and blocks toll-like receptors on plasmacytoid dendritic cells, which leads to a reduced activation of the dendritic cells and a reduction in inflammatory process [15].

Symptoms

In early stages of hydroxychloroquine retinopathy, patients are asymptomatic. When vision is impacted it can include:

- paracentral scotoma (early)
- decreased color vision (early)
- reduced acuity (late)
- reduced peripheral vision (late)
- reduced night vision (late)

Signs

The classic sign of hydroxychloroquine retinopathy is bilateral “bull’s-eye” appearance of the macula due to disruption of the retinal pigmented epithelium. However, this finding occurs late in the toxicity and once it occurs the likelihood of permanent vision loss is significant so it is not useful as a screening tool.

Pathophysiology

The complete mechanism of hydroxychloroquine retinal toxicity not known, however, studies have shown that the drug impacts ganglion cell metabolism and binding of melanin in RPE cells [16].

Medication Dosage

Studies show that cumulative dose may be more important than daily dosage but since a higher daily dose will lead to a higher cumulative dose more rapidly than a lower daily dose [13].

Presenting Antigens

Toll-like receptor 9, recognizes DNA-containing immune complexes and leads to the production of interferon and causes the dendritic cells to mature and present antigens to T cells [15].

Vitreomacular Update for the Primary Care OD

It is difficult to predict exactly which patients will develop retinal toxicity, however, high-risk characteristics include the following [13]:

- daily dose greater than 400 mg
 - a daily dosage over 6.5 mg/kg ideal body weight
 - In patients who weigh < **135lbs daily dose should be adjusted**
 - total cumulative dose of more than **1,000 g**
- medication use longer than five years
- concomitant renal or liver disease (because the drug is cleared by both routes)
- underlying retinal disease or maculopathy
- age greater than 60 years

Monitoring Guidelines

Updated guidelines state that due to sensitivity, specificity and reliability issues, the following tests are **not recommended** to be utilized as screening tools:

- Amsler grid testing
- Color vision testing
- Fundus examination (including photos)
- Full-field electroretinogram (ffERG)
- Eelectrooculogram (EOG)

Current Guidelines Recommend [13]:

A **baseline examination** at the initiation of treatment to include:

1. Thorough ocular examination documenting any **preexisting conditions** and baseline fundus photos,
2. Humphrey visual field central 10-2 white-on-white pattern
3. At least one of the following objective tests:
 - Fundus autofluorescence (FAF)
 - Multifocal electroretinogram (mfERG) or
 - Spectral domain OCT (SD-OCT)

Years 1-5 screening should include:

1. Annual ophthalmic examination
2. Additional testing if abnormalities are noted on baseline examination or for patients who are at higher risk
 - a. Humphrey visual field central 10-2 white-on-white pattern
 - b. Fundus autofluorescence (FAF)
 - c. Multifocal electroretinogram (mfERG) or
 - d. Spectral domain OCT (SD-OCT)

After five years of treatment screening should include:

1. Annual ophthalmic examination
2. Humphrey visual field central 10-2 white-on-white pattern
3. At least one of the following objective tests:

- Fundus autofluorescence (FAF)
- Multifocal electroretinogram (mfERG) or
- Spectral domain OCT (SD-OCT)

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