**Oral MS Drug May Increase Risk for Macular Edema**

**A report from the North American Neuro-Ophthalmology Society (NANOS) and the AAO**

**ONE Neuro-Ophthalmology Committee***
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Data from recent multinational Phase 2 and 3 clinical trials of fingolimod (Gilenya, Novartis) suggest an association of the agent to a low risk of cystoid macular edema (CME). Fingolimod is the first oral medication approved by the U.S. FDA for relapsing forms of MS and is an immunomodulator that regulates lymphocyte distribution, reducing lymphocyte recirculation from lymphoid tissue to blood and peripheral tissues. A two-year FDA clinical trial compared fingolimod with placebo and another one-year trial compared fingolimod with interferon beta-1a. Although several clinical trials to date have shown fingolimod to be well tolerated, side effects have included bradycardia, headache, upper respiratory tract infection, shortness of breath, diarrhea and nausea. In the two-year trial, macular edema occurred in 0.4 percent of patients treated with fingolimod and 0.1 percent who received the placebo. Study patients were monitored with medical histories, visual acuity, contrast sensitivity, dilated ophthalmoscopy, optical coherence tomography (OCT), and had ophthalmic examinations at 1, 3, 6, 12 and 18 months.

Compared to placebo, Fingolimod reduced the MS relapse rate and increased the percentage of patients without a MS relapse in both studies. The differences were statistically significant ($P <$ .001).

Amongst all of the Phase II, Phase III, and extension studies of fingolimod, sixteen study patients developed macular edema during the study period. One patient had associated branch retinal vein occlusion with macular edema. Four patients had a prior history of uveitis. Only 2 of the patients on the currently approved 0.5mg tablet developed macular edema (ME), (0.2%), while the incidence was 1.1% in patients on the non-approved 1.25mg dosage. Twelve patients with ME presented with blurred vision or decreased acuity and 75% presented within the first four months of treatment. ME usually resolved after discontinuation of fingolimod.

**Warnings, recommendations:**
The FDA requires the manufacturer to include warnings and precautions on labeling of fingolimod. Due to effects on the sino-atrial node, fingolimod is associated with a slowing of the heart rate, which is maximal in the first six hours after the first dose and returns to normal within 2-4 weeks. Therefore it is recommended all patients be observed in a physician's office for six hours after the first dose.

Although the current product packaging suggests patients should undergo ophthalmic examination prior to or within several weeks before treatment initiation, as well as three or four months after initiation of fingolimod therapy, there is no current evidence based recommendation for screening frequency or content.*

Despite the lack of an evidence-based recommendation, and a low, but still not completely defined association of retinal dysfunction after starting fingolimod, at this time NANOS and the AAO ONE Committee believe that the following recommendations are reasonable practice options.

1. A screening evaluation for pre-existing uveitis or macular or retinal vascular disease prior to starting, or within the first few weeks of starting fingolimod should be considered.
2. A single re-evaluation at 3-4 months of therapy is recommended. All of the reported cases of ME occurred within this initial time frame, so the role of further repeated evaluation has not been established.
3. Patients should be advised that the incidence of macular edema is low (~2/1000) with the current recommended dosage, but if there is a past history of uveitis, the incidence may be as high as 20%. Diabetes and retinovascular disease may be additional risk factors, but the additional possible risk they produce for macular edema remains unknown at this time.
4. A visual acuity check and a complete eye exam including adilated fundus exam is a reasonable ophthalmic screening protocol. As up to 25% of ME noted during the studies was asymptomatic, lack of subjective symptoms does not necessarily indicate absence of ME.
5. Patients with abnormalities on exam or unexplained decreased visual acuity might benefit from diagnostic imaging with macular OCT.

References:


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*Disclaimer: The recommendations contained in this report should not be construed as a standard of care, as there is insufficient evidence to support specific recommendations at this time