Oral Fluorescein Angiography in Patients With Choroidal Neovascularization and Macular Degeneration

Dirk-Uwe Bartsch, PhD; Abbas Elmusharaf, MD; Mohamed El-Bradey, MD; William R. Freeman, MD

**OBJECTIVE:** To evaluate image quality of oral fluorescein angiography in patients with age-related macular degeneration and choroidal neovascularization.

**MATERIALS AND METHODS:** Twenty four patients with proven choroidal neovascularization were examined in a prospective observational case series. Confocal oral and intravenous fluorescein angiography were performed using the Heidelberg Retina Angiograph. Oral and intravenous image quality were compared in a masked fashion.

**RESULTS:** Choroidal neovascularization could be diagnosed in all patients using intravenous angiograms. Oral fluorescein angiography accurately detected the presence or absence of choroidal neovascularization in all patients and could determine the classification of choroidal neovascularization, location, and extent and borders in 20 (83.3%) of 24 patients. Early, mid, and late phases of oral angiograms occurred at 8, 15, and 26 minutes, respectively.

**CONCLUSION:** Oral fluorescein angiography using the confocal Heidelberg Retina Angiograph allowed detection of choroidal neovascularization in all patients in this study. Visualization of extent and type of choroidal neovascularization was possible in most eyes with choroidal neovascularization. These findings suggest oral angiography is an excellent screening tool for choroidal neovascularization and allows guidance of treatment in the majority of cases.


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**INTRODUCTION**

A major problem in the management of age-related macular degeneration is the early detection of choroidal neovascularization, and for this purpose, fluorescein angiography is extremely helpful. Dyer et al. showed in eyes previously treated for choroidal neovascularization, the absence of clinical signs of recurrent new vessel formation did not completely exclude recurrent choroidal neovascularization. Their study highlighted the importance of using specific fluorescein angiography to detect choroidal neovascularization since 59% of choroidal
neovascularization would have been undetected based on clinical criteria alone.

Most investigators agree the gold standard for detecting choroidal neovascularization is fluorescein angiography. Indocyanine green may offer additional information in certain clinical situations.\(^2\) It has been suggested indocyanine green may detect or localize choroidal neovascularization in eyes in which fluorescein angiography detects an abnormality but cannot localize it precisely. In addition, Flower et al.\(^3\) found indocyanine green imaging with conventional fundus cameras may have false hyperfluorescence artifacts. Thus, there may be a disparity between fundus camera and scanning laser ophthalmoscope indocyanine green imaging of retinal pigment epithelium detachments. However, both digital fundus cameras and digital scanning laser ophthalmoscopes have the advantage of allowing image enhancement, which may improve the utility of oral fluorescein angiography.\(^4,6\)

Burr\(^1\) first studied oral fluorescein angiography in 1910 using ophthalmoscopy to detect fluorescence. Subsequently, Kelly and Kincaid and others were able to describe macular problems with oral fluorescein angiography; however, the resolution and sensitivity of film-based oral fluorescein angiography has been widely regarded as inferior to intravenous studies.\(^8,9\) Similarly, oral angiography may be used to detect leakage from diabetic macular edema\(^10\) and is effective and safe.\(^9\)

In our previous study, oral fluorescein angiography taken with a scanning laser ophthalmoscope was compared to oral fluorescein angiography taken with a fundus camera.\(^11\) However, the utility of oral fluorescein angiography taken with a scanning laser ophthalmoscope for the diagnosis and treatment of choroidal neovascularization in patients with age-related macular degeneration was not examined. The amount of information needed to guide treatment of choroidal neovascularization depends on the location of the disease. The Macular Photocoagulation Study (MPS)\(^12-14\) has shown that for extrfoveal neovascularization, the membrane must be able to be localized and be relatively well defined before laser therapy. For subfoveal neovascularization, similar considerations have applied. In most cases, subfoveal choroidal neovascular membranes are treated with photodynamic therapy.\(^15\) Criteria for such treatment include being able to detect neovascularization and localize the borders well enough to include them in the treatment area. However, although patients with occult neovascularization tend to respond better with photodynamic therapy than healthy individuals,\(^16\) those receiving photodynamic therapy do not retain as much vision as patients with predominant classic neovascularization receiving photodynamic therapy.\(^15,16\)

The current study was undertaken to assess whether oral angiography would be sensitive enough to detect choroidal neovascularization and whether sufficient information to guide treatment could be obtained. We hypothesized that the confocal scanning laser ophthalmoscope, because of its high contrast and ability to excite at the maximum efficiency\(^17-22\) and confine images to one plane (Figure 1), would give high enough quality images to screen for choroidal neovascularization and determine whether it would be treatable.

**MATERIALS AND METHODS**

Patients were recruited from the patient population of the retina clinic at the University of California San Diego (UCSD) Shiley Eye Center. Twenty-four eyes of 24 consecutive patients who had undergone both oral and intravenous angiography within a 1-week period were studied. Patients were selected prospectively from the pool of patients at the UCSD Shiley Eye Center. In
each case, the oral angiogram was obtained within 7 days of an intravenous angiogram. All patients had intravenous fluorescein angiography at the initial examination. Twenty-one patients were analyzed using a confocal scanning laser ophthalmoscope camera (Heidelberg Retina Angiograph [HRA], Heidelberg Engineering, Carlsbad, CA) and 3 were analyzed using a conventional fundus camera (Topcon 50VT, Topcon Inc, Paramus, NJ). Details of the scanning laser ophthalmoscope have been described previously.17,18 There were 4 cases of untreated classic choroidal neovascularization, 7 occult cases, and 3 mixed. An additional 6 eyes were evaluated postconventional laser ablation of choroidal neovascularization and an additional 4 eyes photodynamic therapy treatment. Of the 24 eyes, the location was as follows: 1 juxtapapillary, 1 juxtapapillary, 4 extrafoveal, and 18 subfoveal choroidal neovascular membranes.

To administer sodium fluorescein orally, 2 ampules of 2 mL (250 mg/mL, Fluoresceite, Alcon Laboratories, Ft Worth, TX) each were mixed with slightly sweetened orange juice. Patients drank the mixture with a straw to prevent staining of their teeth and gums followed by another cup of juice to mask the taste.

Angiographic image quality was assessed in a masked fashion. Angiograms taken on the HRA used stereo views performed similarly to a conventional fundus camera. Regardless of whether the stereo views were taken with the fundus camera or the HRA, the definitions of classic versus occult neovascularization were based on leakage brightness as defined by the criteria of the TAP (Treatment of Age-Related Macular Degeneration With Photodynamic Therapy) study.25 The definitions were used for both intravenous and oral angiograms. The study was reviewed and approved by the UCSD Human Research Protection program.

For each examination, one of the authors (WRF) selected representative frames for analysis. All HRA images were stored digitally and exported for analysis and classification to remove patient name, angiography timing, and other identifying markers. Angiograms taken with the fundus camera on 35-mm film in 3 patients were digitized using a high-resolution Canon FS-2710 slide scanner at 2000 dpi. All of the authors determined the quality of the digitized images was high and adequately represented, allowing the information seen on the original film angiogram to be viewed. A mask was placed over any identifying characteristics that would inform a reviewer whether the intravenous images were originally taken from the 35-mm film or digital images from the HRA, as opposed to the oral images taken with the HRA. Angiographic quality was rated on a scale of 0-3 as described elsewhere.11 In brief, grade 0 indicated there was no usable image, grade 1 indicated mild image quality, grade 2 indicated good quality, and grade 3 indicated excellent image quality. Similar images from oral and intravenous fluorescein angiography were compared to establish timing phases for the oral fluorescein angiography.

Statistical analysis was performed using the JMP program (SAS Institute, Cary, NC). Wilcoxon’s 2-sampled signed rank test was used to compare the image quality grades of intravenous and oral fluorescein angiography. The sensitivity of oral fluorescein angiography was determined as the number of correct positives divided by the sum of correct positives and false negatives. Similarly, specificity was determined as the number of correct negatives divided by the sum of correct negatives and false positives.

**RESULTS**

Sixteen eyes of 24 patients (19 women and 5 men) with age-related macular degeneration were diagnosed with choroidal neovascularization by intravenous fluorescein angiography. Using intravenous angiography as the gold standard, oral fluorescein angiography accurately detected the presence or absence of choroidal neovascularization in 20 (83.3%) of 24 patients. Furthermore, the oral fluorescein angiography image quality in 20 (83.3%) patients was deemed acceptable (grades 2 or 3). The remaining 4 angiograms were of grade 0 (no suitable image recorded). The grade 2 images in 2 patients still clearly demonstrated the area of hyperfluorescence and leakage. However, the precise origin of leakage was poorly interpreted (Table 1). Wilcoxon’s 2-sampled signed rank significance test was used to compare the oral and intravenous images and

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**Table 1. Comparison of Image Quality for Oral and Intravenous Fluorescein Angiography**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Image Quality</th>
<th>No. (%) Intravenous</th>
<th>No. (%) Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Poor</td>
<td>0 (0)</td>
<td>4 (16.6)</td>
</tr>
<tr>
<td>1</td>
<td>Fair</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>Good</td>
<td>3 (12.5)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>3</td>
<td>Excellent</td>
<td>21 (87.5)</td>
<td>18 (75)</td>
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*N=24.*

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<tr>
<th>Patient No.</th>
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<th>Oral FA Evaluation Assessment for Treatment</th>
<th>Oral FA Detection of CNV</th>
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<tr>
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<td>100% well defined</td>
<td>Yes</td>
</tr>
<tr>
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<td>100% well defined</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
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<td>100% poorly defined</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
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<td>Inability to assess†</td>
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</tr>
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<tr>
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<td>Postphotodynamic therapy no. 1, no recurrence</td>
<td>Postphotodynamic therapy no. 1, no recurrence</td>
<td>No</td>
</tr>
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</table>

FA=fluorescein angiography; CNV=choroidal neovascularization
*In 20 of 24 patients, a concordance between oral and intravenous fluorescein angiography in terms of utility to assess treatment was shown. The patients in whom no concordance was shown were patients 6, 11, 18, and 19.
†One eye per patient.
‡Inability to assess because of inadequate image quality.

found a P value of .0007. The sensitivity of oral fluorescein angiography was 87.5% and the specificity was 75%, with an overall accuracy of 83.3%.

Using MPS criteria, the type of choroidal neovascularization membrane could be determined on oral angiography in 20 of the 24 eyes imaged. Four eyes were classic, 5 were occult, 3 were mixed, 4 postlaser treatment eyes had no recurrence, 2 postphotodynamic therapy eyes were determined to have recurrence, and 2 postphotodynamic therapy eyes were correctly determined to be inactive (Table 2).

The correlation in timing between the early, middle, and late phases of oral angiogram and intravenous fluorescein angiography were determined. Three separate phases of the oral fluorescein angiogram similar in appearance to the three phases of the intravenous
angiogram could be distinguished, but the different phases of the oral fluorescein angiograms were delayed compared to the intravenous angiogram. Figure 2 shows examples of the phase findings obtained with oral fluorescein angiography. In all cases, the photographer observed the fundus after fluorescein ingestion; therefore, the first recognition time indicates the first appearance of the fluorescence.

The early phase was present 7-9 minutes (median±SD: 8.45±3.44, range: 3.45-16.83) after ingestion of the dye (Table 3); the artery and the veins were filled at the same time with the absence of lamellar flow within 1 minute after the dye appeared in the retinal vessels. The start of the filling of the artery and the veins was simultaneous, with no early laminar flow in the veins. The choroidal neovascularization could be identified angiographically as a hyperfluorescent area at the 15-20 minute time point, termed mid phase of the oral angiogram. The mid phase (median±SD: 15.28±5.00, range: 8.15-25.21) was characterized by the behavior of the dye in the area of the choroidal membrane. The late phase (median±SD: 26.73±6.19, range: 15.36-36.93) was defined by the leaking characteristics; the choroidal neovascularization showed clear leakage on oral fluorescein angiography at 25-30 minutes, which was the time when
prominent leakage was present and retinal vessels were not filling prominently. In the majority of cases, the quality of the late-phase angiogram after oral fluorescein administration was actually better than after intravenous angiography (Figure 2). Four (16.7%) of 24 patients had image quality that was not good enough to provide useful information to study and record the time phase of oral fluorescein angiography.

No adverse major reactions occurred after oral fluorescein administration. One patient reported nausea, but none of the patients reported vomiting, skin rash, or respiratory problems.

**DISCUSSION**

Photographic documentation of retinal circulation by means of an intravenous injection of sodium fluorescein has been widely used since reported by Novotny and Alvis in 1961. A serious reaction to intravenous fluorescein may occur without warning in patients without allergic history; fatal reactions can occur in 1 in 222,000 cases.25,26

In patients in whom intravenous injections are contraindicated, it is difficult to adequately visualize the retinal and choroidal circulations to diagnose and treat pathology.27 Oral fluorescein angiography has been proposed as an alternative to intravenous angiography and its complications.27-30 A mild skin reaction has been reported with an oral dose in a patient with a personal and familial history of atopic eczema.31 However, the adverse reaction rate and severity is less with oral than with intravenous fluorescein angiography. The phenomenon of lower incidence of adverse reaction to an orally administered agent versus the intravenous route has been well documented in the case of penicillin.32

Previous studies of oral fluorescein angiography have used a conventional fundus camera and considered that oral angiography images were useful only in late images, as with patients with cystoid macular edema, central serous retinopathy, and retinal pigment detachment. While we did not compare scanning laser ophthalmoscopy to digital fundus photography, we believe the quality of oral fluorescein angiography with digital fundus photography will be worse than with a scanning laser ophthalmoscope due to the higher light yield of a scanning laser ophthalmoscope.17,18,33 Nevertheless, digital fundus photography can be expected to yield better image quality than film photography due to the availability of digital enhancements such as frame averaging and other effects.4

The results of this study indicate oral fluorescein angiography with a confocal scanning laser ophthalmoscope yielded a high photographic success rate and the quality of the photographs obtained was excellent for determining the presence or absence of choroidal neovascularization in 100% of patients. In this rela-
tively small study, the type of choroidal neovascularization membrane could be determined by MPS criteria including classification (occult versus classic), location, extent, and borders using oral angiography in 87.5% of patients (14 of 16 cases). In addition, the time phase of oral angiograms could be characterized in patients with choroidal neovascularization. The 8-9 minute oral time was equivalent to the early intravenous phase in appearance of dye-filled vessels against a nonfluorescent background, and the mid-phase intravenous angiogram appeared similar to the oral fluorescein angiogram at an average of 8.45 minutes. Finally, the late oral phase (27 minutes) was equivalent in appearance to the 10-minute intravenous phase. While the appearance of dye in our study population showed a large variation, the variation appeared to be uniform for the patient. This means that a patient with a slow arrival of dye in the early phase had a slow appearance of dye in all three phases.

This study showed a high photographic success rate and indicated the quality of the photography required for diagnosing and guiding treatment in eyes with choroidal neovascularization was generally adequate. In some cases, the oral angiograms were strikingly similar in quality to the intravenous angiograms. Interestingly, although the quality of intravenous angiography was generally superior to oral angiography in the early and mid phases, leakage often could be seen better after oral fluorescein angiography in the late-phase images. It is possible this is because a larger dose of fluorescein is administered or the time the late images are acquired is much later than during intravenous angiography. Oral angiography allowed determination of the extent of classic neovascularization adequately to assess whether lesions were more than 50% classic. In addition, it allowed assessing whether the lesions were classic, occult, or mixed. The location of the neovascular membrane also could be determined as extrafoveal, subfoveal, or juxtafoveal. There were four cases in which the oral angiogram could not detect the precise extent nor clearly define the borders of the membrane. In these cases, the angiogram would have to be repeated with dye administered intravenously.

CONCLUSION

Oral fluorescein angiography using the confocal scanning laser ophthalmoscope (HRA) is an excellent screening tool in patients with suspected choroidal neovascularization and would allow the ophthalmologist to treat the majority of patients. A larger study is required to determine more precisely the number of lesions that might require additional oral angiography for treatment.

REFERENCES


