

# Erdaftinib-associated Central Serous Chorioretinopathy: A Case Report

**Sierra N. Blanchard, OD**  
**Suzzane S. Li, OD, FAAO**  
**Danielle L. Weiler,**  
**OD, FAAO, Diplomate**

Optometry Section,  
Southern Arizona VA  
Health Care System  
Tucson, Arizona

Southern California  
College of Optometry  
Fullerton, California

## ABSTRACT

Erdaftinib is a pan-fibroblast growth factor receptor (FGFR) kinase inhibitor that has been approved for the treatment of patients with metastatic or locally advanced urothelial carcinoma. It is also being examined for the treatment of other types of cancer. This oral chemotherapeutic agent carries a warning for potential ocular adverse reactions including treatment-related central serous retinopathy and dry eyes. This case report describes an 88-year-old Caucasian male who was co-managed in the eye clinic over the course of treatment with erdaftinib for metastatic urothelial carcinoma. The patient developed asymptomatic episodes of relapsing and remitting treatment-related bilateral central serous retinopathy. It is crucial for eye care providers to recognize the potential ocular adverse events related to erdaftinib, its drug class, and medications that target similar pathways. Effective communication and careful co-management with oncology is essential for providing quality care to this subset of patients. With care coordination, effective yet tolerable dosing may provide the patient with a better survival rate and improved quality of life.

## KEY WORDS:

Erdaftinib, treatment-related central serous retinopathy, urothelial carcinoma, fibroblast growth factor receptor (FGFR) inhibition

## INTRODUCTION

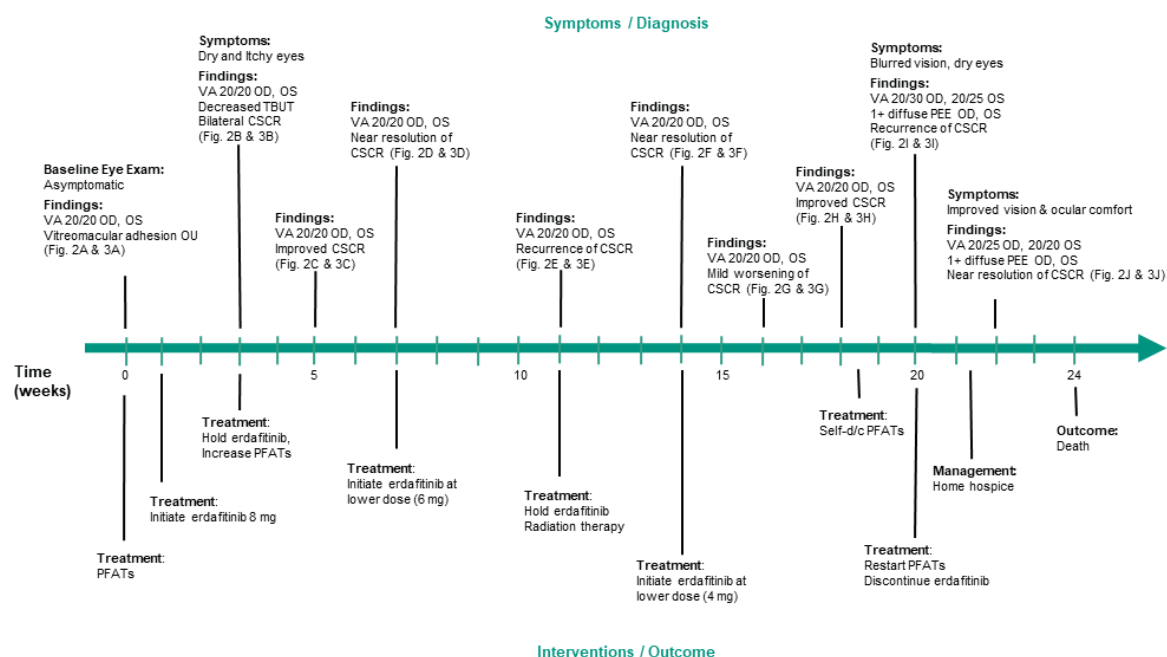
Erdaftinib (Balversa, Janssen Pharmaceuticals, Horsham, PA) is the first Food and Drug Administration (FDA)-approved oral fibroblast growth factor receptor (FGFR) kinase inhibitor for adults with metastatic or locally advanced urothelial carcinoma with FGFR2 or FGFR3 mutations that has progressed with prior chemotherapy.<sup>1-4</sup> The term urothelial carcinoma refers to malignancy arising from uroepithelial cells lining the bladder, ureters, urethra, or renal pelvis.<sup>5</sup> When this medication was approved for use by the FDA in 2019, one of the black box warnings was treatment-related central serous retinopathy, a preferred term that includes chorioretinopathy, retinal detachment, and detachment of the retinal pigment epithelium,<sup>6</sup> which occurs in 25% of patients with a median time of first onset of 50 days.<sup>1</sup> Patients with erdaftinib-related central serous retinopathy can be asymptomatic or present with sudden onset of bilateral blurred vision.<sup>1,7</sup> The mainstay of treatment is to interrupt, discontinue, or lower the dose of erdaftinib based on the severity of the central serous retinopathy.<sup>5</sup> Dry eye is also a potential ophthalmic adverse event and is observed in 28% of patients during treatment.<sup>1</sup> There are no known risk factors or genetic predilections that can be used to predict which patients will be affected by either adverse reaction. Other black box warnings include hyperphosphatemia and embryo-fetal toxicity.<sup>1</sup>

Despite these black box warnings and known ocular adverse reactions widely published within the oncology literature, the ophthalmic literature is limited.<sup>7-9</sup> This case report presents a case of bilateral serous retinopathy secondary to the use of erdaftinib, introduces eye care providers to erdaftinib, and reviews the effects of erdaftinib on the eye and vision. There is no identifiable health information included in this case report.

## CASE REPORT

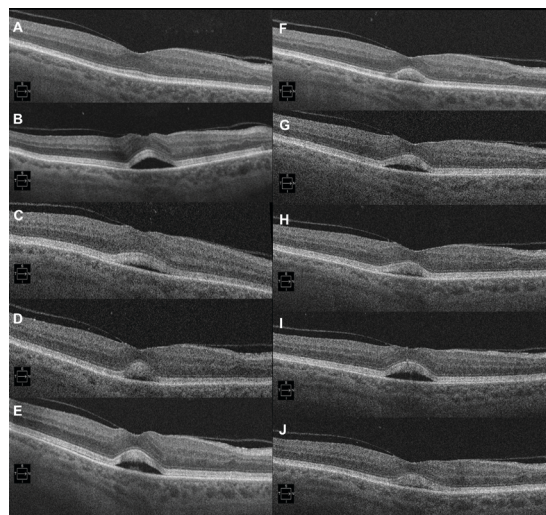
An 88-year-old Caucasian male was referred from the oncology department for a baseline eye exam prior to initiating erdafitinib. At the time of presentation, the patient reported clear vision in both eyes and denied any ocular complaints. His ocular history was significant for pseudophakia with essential emmetropia in both eyes. His medical history was remarkable for metastatic urothelial carcinoma with metastases to the liver, lungs, and bladder. Additional medical history included rhinitis, chronic obstructive lung disease, coronary artery disease, sleep apnea, osteopenia, colonic polyps, hypogonadism, hyperlipidemia, hypertension, lower back pain, and transient ischemic attack for which he used aspirin, albuterol inhaler, atorvastatin, baclofen, docusate, furosemide, hydrocodone/acetaminophen, losartan, metoprolol, and ondansetron. Best-corrected visual acuities were 20/20 in the right and left eyes. Slit lamp examination was remarkable for bilateral pseudophakia. Dilated funduscopy and baseline optical coherence tomography were within normal limits except for mild focal vitreomacular adhesion in the right eye and mild focal vitreomacular traction in the left eye with a subfoveal choroidal thickness of 266 microns in the right eye and 260 microns in the left eye (Figures 2A and 3A). Preservative-free artificial tears were prescribed four times daily for dry eye prophylaxis. One week after this baseline eye exam, the oncology team initiated erdafitinib 8 mg daily, and recommended a one-month follow-up eye exam. Subsequent follow-up visits were scheduled while the patient was co-managed with the oncology team. Throughout the clinical course (Figure 1), there were asymptomatic episodes of Grade 1 relapsing and remitting bilateral central serous retinopathy (Table 1, Figures 2 and 3) correlated with erdafitinib dose modifications and interruptions. As the patient became increasingly ill, he was unable to instill artificial tears, resulting in a mild reduction in vision at week 20 due to dryness of the ocular surface. Ultimately, the patient died 24 weeks after the initial presentation.

**Figure 1:** Clinical Timeline. An 88-year-old male developed bilateral treatment-related central serous retinopathy following the initiation of erdafitinib for metastatic urothelial carcinoma with metastases to the liver, lungs, and bladder.

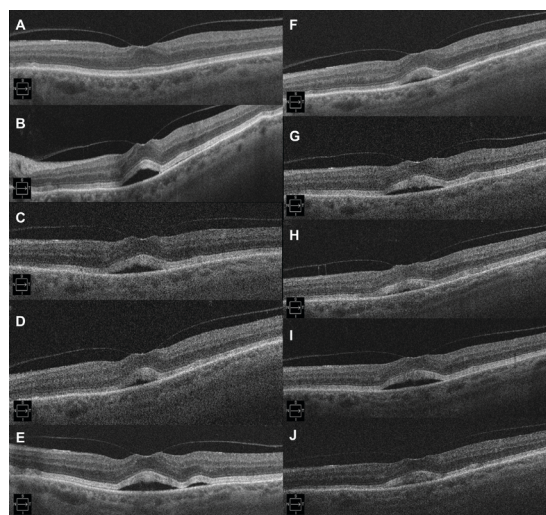


VA = visual acuity; OD = right eye; OS = left eye; OU = both eyes; TBUT = tear break-up time; CSCR = central serous retinopathy; PFATs = preservative-free artificial tears; PEE = punctate epithelial erosions; PCO = posterior capsular opacification

**Figure 2:** Spectral-domain optical coherence tomography using high-definition raster acquisition of the right eye over the clinical course with the associated central subfield thickness ( $\mu\text{m}$ ). A: Baseline. B: Initial occurrence of bilateral treatment-related central serous retinopathy (CSR), 2 weeks following the initiation of erdafitinib 8 mg. C: Improved CSR, 2 weeks after holding erdafitinib. D: Improvement/stable CSR, 4 weeks after holding erdafitinib. E: Relapse of CSR, 4 weeks after the re-initiation of erdafitinib at a lower dose (6 mg). F: Improvement of CSR, 3 weeks after holding erdafitinib. G: Worsening of CSR, 2 weeks after the re-initiation of erdafitinib at a lower dose (4 mg). H. Improved CSR, 4 weeks after restarting erdafitinib at 4 mg. I: Relapse of CSR, 6 weeks after restarting erdafitinib at 4 mg. J: Improvement of CSR, 2 weeks after the discontinuation of erdafitinib.



**Figure 3:** Spectral-domain optical coherence tomography using high-definition raster acquisition of the left eye over the clinical course. Images taken at the same times as components of Figure 2.



**Table 1:** Definitions of the severity of treatment-related central serous retinopathy and correlated manufacturer's recommendations for erdafitinib dose modification [Adapted from erdafitinib prescribing guidelines, Janssen Pharmaceuticals<sup>1</sup>]

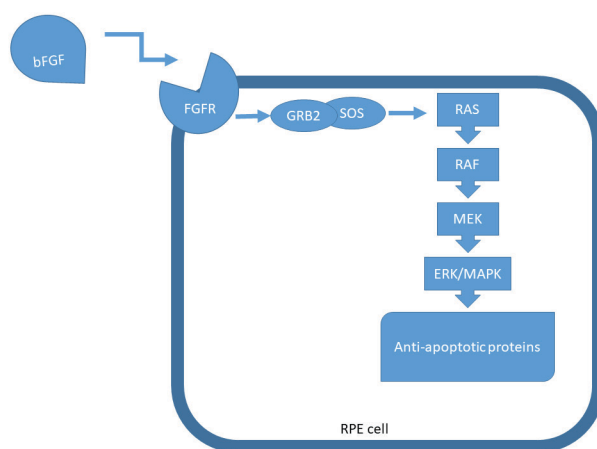
Severity	Clinical Signs or Symptoms	Erdafitinib Dose Modification Recommendation
Grade 1	Asymptomatic; clinical or diagnostic observations only	Withhold until resolution. If resolution occurs within 4 weeks, resume at the next lower dose level. If there is no recurrence for a month, consider re-escalation. If the condition remains stable for 2 consecutive eye exams but is not resolved, resume at the next lower dose level.
Grade 2	Visual acuity 20/40 or better or $\leq 3$ lines of decreased vision from baseline	Withhold until resolution. If resolution occurs within 4 weeks, may resume at the next lower dose level.
Grade 3	Visual acuity worse than 20/40 or $> 3$ lines of decreased vision from baseline	Withhold until resolution. If resolution occurs within 4 weeks, may resume at two dose levels lower. If the condition recurs, consider permanent discontinuation.
Grade 4	Visual acuity 20/200 or worse in affected eye	Permanently discontinue.

## DISCUSSION

Erdafitinib is a novel, small-molecule FGFR-kinase inhibitor that has been approved for second-line treatment of advanced local or metastatic urothelial carcinoma or first-line treatment of urothelial cancers susceptible to FGFR2 or FGFR3 gene alteration.<sup>2-4</sup> It is also being examined for treatment of cholangiocarcinoma, liver cancer, non-small cell lung cancer, prostate cancer, lymphoma, and esophageal cancer.<sup>10</sup> The FDA granted accelerated approval for the use of erdafitinib to treat advanced urothelial carcinoma in 2019 due to its efficacy in a phase 2 clinical trial, as reported by Loriot et al.,<sup>2</sup> making it the first FDA-approved FGFR-targeting drug.<sup>11</sup> The recommended initial dose for erdafitinib is 8 mg by mouth daily. If the patient tolerates the medication after 14–21 days of use, the dose is increased to 9 mg daily.<sup>1,5</sup>

Erdafitinib is known to be a pan-FGFR inhibitor as it binds to and inhibits enzymatic activities of FGFR1, FGFR2, FGFR 3, and FGFR4 receptors.<sup>1,2,4</sup> FGFR is present throughout the retina but is mostly highly expressed in retinal pigment epithelial cells and macroglial cells.<sup>12</sup> Inhibition of FGFR can affect multiple downstream signaling cascades, including phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (the PI3K/AKT/mTOR pathway) and the mitogen-activated protein kinase (MAPK) pathway (Figure 4).<sup>8,12-14</sup> Additionally, erdafitinib inhibits other receptors such as RET, CSF1R, PDGFRA, PDGFRB, FLT4, KIT, and VEGFR2.<sup>1,2</sup>

**Figure 4:** Fibroblast growth factor receptor (FGFR) signaling in retinal epithelial cells. Basic fibroblast growth factor in retinal tissue binds to FGFR activating GRB2/SOS. GRB2/SOS then triggers the PI3K/AKT/mTOR and MAPK pathways. Both of these pathways eventually trigger transcription of genes involved in cell maintenance, protection, repair, and survival.



RPE = retinal pigment epithelial; bFGF = basic fibroblast growth factor; FGFR = fibroblast growth factor receptor; GRB2 = growth factor receptor bound protein 2; SOS = son of sevenless protein; RAS = a type of small GTP-binding protein; RAF = a serine/threonine protein kinase; MEK = MAPK/ERK kinase; MAPK = mitogen-activated protein kinase; ERK = extracellular regulated kinase; PI3K = phosphoinositide 3-kinase; AKT = protein kinase B; mTOR = mammalian target of rapamycin

Treatment-related central serous retinopathy is a known class effect of inhibitors of MAPK kinase (MEK).<sup>2, 12, 13, 15, 16</sup> Due to the upstream inhibition of FGFR, the pathogenesis of treatment-related central serous retinopathy is likely to be similar to MEK-related retinopathy.<sup>8, 9</sup> The MAPK pathway has been implicated as the most important FGFR signaling pathway in the retinal pigment epithelium given its responsibility for the maintenance, survival, and repair of retinal pigment epithelial cells.<sup>12</sup> However, the exact pathophysiology of the erdafitinib-related central serous retinopathy remains unknown. Inhibition of the PI3K/AKT/mTOR pathway likely also plays a role as it seems to be involved in the cell's response to oxidative stress.<sup>8, 12</sup> Additionally, aquaporin 1 (AQP1), a protein involved in tight junction integrity and retinal pigment epithelial cell permeability, is mediated through the MAPK pathway.<sup>13, 17, 18</sup> Thus, disruption of these tight junctions may result in subretinal fluid accumulation.<sup>17, 18</sup>

The main limiting factor for oncologists to select erdafitinib as a therapy of choice is its toxicity profile.<sup>19</sup> An ongoing phase 3 clinical trial has the goal of providing conclusive evidence on the long-term safety and efficacy profile of erdafitinib by comparing it to other medications such as vinflunine, docetaxel, or pembrolizumab for patients with FGFR mutated urothelial cancers.<sup>5</sup> It is expected to conclude in November 2021.

In a phase 2 study, ocular adverse events were common with erdafitinib treatment, but these events were mostly mild to moderate and resolved with dose interruption or reduction.<sup>1, 2</sup> Ocular adverse effects was the most common reason for dropping out of the clinical trial,<sup>1</sup> including 3% of patients who had to discontinue treatment with erdafitinib due to severe central serous retinopathy.<sup>1</sup> Dry eye symptoms occurred in 28% of the patients during treatment with erdafitinib, and were Grade 3 in 6% of patients.<sup>1</sup> Therefore, it is recommended that all patients should receive artificial tears to prevent dry eye signs and symptoms.<sup>1</sup> Due to the high prevalence of ocular side effects, the manufacturer's prescribing guidelines recommend co-management with an eye care provider, with a baseline ophthalmic examination prior to initiating erdafitinib and then monthly follow-ups for the first four months of treatment.<sup>1</sup> Each of these ophthalmic examinations should include an assessment of visual acuity, slit lamp examination, funduscopy, and optical coherence tomography.<sup>1</sup> After four months, ophthalmic follow-ups may be extended to every 3 months while the patient is on treatment.<sup>1</sup> In addition, a dilated eye examination with optical coherence tomography is indicated at any point during the treatment course if the patient experiences visual symptoms.<sup>1, 9</sup>

If a patient develops central serous retinopathy, the daily dose of erdafitinib should be withheld on the initial encounter, then modified if the central serous retinopathy resolves within four weeks or remains stable for two consecutive eye exams (Table 1).<sup>1</sup> Typically, erdafitinib-related central serous retinopathy usually resolves with dose reduction or dose interruption (Table 2), and most patients are able to continue therapy.<sup>2, 5, 6</sup> In this case, relapsing and remitting treatment-related central serous retinopathy was noted without full resolution despite dose interruption (Figure 2). Given its stability for two consecutive visits and the potential life-sustaining treatment, the oncology service opted to continue erdafitinib at the lowest dose until the patient's vision was affected. The oncologist and patient must weigh the presence of treatment-related central serous retinopathy and potential for decreased quality of life if vision is affected against its life-sustaining potential. The role of the eye care provider is to co-manage and communicate the presence or absence of ocular side effects to the oncology team following each ophthalmic examination.

**Table 2:** Manufacturer's schedule for erdafitinib dose reduction [Adapted from erdafitinib prescribing guidelines, Janssen Pharmaceuticals<sup>1</sup>]

Dose	1 <sup>st</sup> dose reduction	2 <sup>nd</sup> dose reduction	3 <sup>rd</sup> dose reduction	4 <sup>th</sup> dose reduction	5 <sup>th</sup> dose reduction
9 mg (three 3 mg tablets)	8 mg (two 4 mg tablets)	6 mg (two 3 mg tablets)	5 mg (one 5 mg tablet)	4 mg (one 4 mg tablet)	Stop
8 mg (two 4 mg tablets)	6 mg (two 3 mg tablets)	5 mg (one 5 mg tablet)	4 mg (one 4 mg tablet)	Stop	

## CONCLUSION

Erdafitinib is a relatively new anti-cancer treatment with known ocular adverse events published in the oncology literature. Despite this, the ophthalmic literature has limited information about erdafitinib-related central



serous retinopathy.<sup>7-9</sup> Although erdafitinib is only currently FDA-approved for advanced or metastatic urothelial carcinoma, it is being developed for the treatment of other cancers. Thus, it is crucial for eye care providers to recognize the potential ocular adverse events related to erdafitinib, its drug class, and medications that target similar pathways. Effective communication and careful co-management with oncology is essential for providing quality care to this subset of patients. ●

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#### FINANCIAL DISCLOSURES

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#### CORRESPONDING AUTHOR

Danielle L. Weiler, OD, FAAO, Diplomate – Danielle.Weiler@va.gov

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