Angiogenesis is a common factor in the pathogenesis of cancer and in exudative age-related macular degeneration (AMD). Therefore, angiogenesis inhibition has been developed as a therapeutic strategy. We report 2 cases of recurrent exudative AMD in which oral sorafenib, a tyrosine kinase inhibitor approved for cancer, was added to intravitreal ranibizumab, an antibody to vascular endothelial growth factor. These 2 patients were followed up by determination of visual acuity, fluorescein angiography, fundoscopy, and optical coherence tomography. The visual acuity of 1 patient improved from 20/70 to 20/60 while he was receiving sorafenib therapy; that of the other did not. Marked improvement was noted in both patients on optical coherence tomography. Additionally, both patients appeared to receive some benefit when low-dose oral sorafenib was used as monotherapy after its initial addition to ranibizumab therapy. Randomized trials of adding sorafenib to standard therapy for patients with neovascular AMD should be considered.


AMD = age-related macular degeneration; IC50 = 50% inhibitory concentration; OCT = optical coherence tomography; PED = pigment epithelial detachment; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor

We describe 2 patients with exudative AMD who needed multiple ranibizumab injections and who elected to have off-label sorafenib added to their standard treatment in an attempt to decrease the number of intraocular injections.

REPORT OF CASES

The Mayo Clinic Institutional Review Board approved this study of 2 patients with exudative AMD in whom ranibizumab therapy was combined with sorafenib.

CASE 1

An 83-year-old man was followed up for recurrent exudative AMD in his right eye (his left eye had a disciform scar with 20/600 vision). He had undergone multiple intraocular injections of bevacizumab and ranibizumab during the past 2 years (Figure 1, A). An initial fluorescein angiogram showed leakage consistent with a mainly occult neovascular membrane (Figure 1, B). His visual acuity was 20/70. Fundoscopy showed intraretinal fluid with cystoid changes. Optical coherence tomography (OCT) revealed retinal thickening with cystic changes (Figure 1, C). Because the patient wanted to decrease the number of intraocular injections, he elected to undergo an injection of intravitreal ranibizumab in conjunction with oral sorafenib, 200 mg, 3 times a week for 5 weeks. At 5-week follow-up, his visual acuity had improved to 20/60, and OCT showed 1 small residual cystoid space (Figure 1, D). One month after the patient discontinued sorafenib therapy, his vision decreased to 20/70, and OCT showed a recurrence of obvious intraretinal fluid (Figure 1, E). The patient elected to use oral sorafenib alone. After 1 month, the patient’s vision improved to 20/50, and OCT showed a marked diminution in the intraretinal fluid (Figure 2, F). The patient stated that after the initial dose of sorafenib, he had mild acral dermatitis, but it resolved spontaneously. He...
CASE 1

An 80-year-old man with recurrent exudative AMD in his left eye had undergone 8 injections of ranibizumab during the past year (Figure 2, A). His visual acuity was 20/30 in his left eye and 20/20 in his right eye. Initial fluorescein angiography had confirmed leakage consistent with a neovascular membrane (Figure 2, B).

Fundoscopy showed confluent soft drusen, intraretinal hemorrhage, and pigment epithelial detachment (PED) with an occult choroidal neovascular membrane involving the fovea. Additionally, OCT revealed PED and intraretinal cystoid spaces (Figure 2, C). The patient was given an injection of ranibizumab and returned 1 month later. Cystoid spaces were still evident, and his vision had decreased to 20/40 (Figure 2, D). He opted to take sorafenib, 200 mg, 3 times a week for a month because he wanted to avoid further intraocular injections. One month later, his visual acuity remained stable, and OCT showed improvement with resolution of the intraretinal fluid and a decrease in the size of the PED (Figure 2, E).

CASE 2

An 81-year-old man with recurrent exudative AMD in his left eye had undergone 8 injections of ranibizumab during the past year (Figure 2, A). His visual acuity was 20/30 in his left eye and 20/20 in his right eye. Initial fluorescein angiography had confirmed leakage consistent with a neovascular membrane (Figure 2, B).

Fundoscopy showed confluent soft drusen, intraretinal hemorrhage, and pigment epithelial detachment (PED) with an occult choroidal neovascular membrane involving the fovea. Additionally, OCT revealed PED and intraretinal cystoid spaces (Figure 2, C). The patient was given an injection of ranibizumab and returned 1 month later. Cystoid spaces were still evident, and his vision had decreased to 20/40 (Figure 2, D). He opted to take sorafenib, 200 mg, 3 times a week for a month because he wanted to avoid further intraocular injections. One month later, his visual acuity remained stable, and OCT showed improvement with resolution of the intraretinal fluid and a decrease in the size of the PED (Figure 2, E).

has had no other problems and continues to take low-dose sorafenib therapy.

DISCUSSION

Vascular endothelial growth factor is implicated in the development of choroidal neovascularization and some forms of cancer.\(^6\)\(^7\) On the basis of this observation, VEGF antagonists are used as treatment of angiogenic diseases.\(^8\)

Currently, only pegaptanib and ranibizumab have been approved by the Food and Drug Administration for treating neovascular AMD, but intravitreal bevacizumab has also been used off label with reported success.\(^1\) Sorafenib and other tyrosine kinase inhibitors have been approved for treatment of certain cancers. Because sorafenib is a strong inhibitor of VEGFR signaling and has a long half-life, we discussed the off-label use of sorafenib with these patients who wanted to undergo fewer intraocular injections.

The 200-mg dosage of sorafenib 3 times a week is much lower than the dosage of 800 mg/d used in patients with cancer. We chose this dosage because very low doses inhibit VEGFR. An oral dose of 200 mg of sorafenib has a half-life of 29.5 hours and a maximum concentration of 1700 nM. This concentration is 18 times higher than the IC50 for VEGFR2 and 65 times higher than the IC50 for VEGFR1; thus, 1 dose should have sufficient inhibitory effect on VEGFR2 for 2 or 3 days.\(^5\)\(^6\)

Both our patients experienced stability or improvement in vision and a marked improvement on OCT after sorafenib therapy was added to the regimen. Case 1 revealed a marked improvement in intraretinal edema 1 month after taking sorafenib. After this patient discontinued sorafenib therapy, intraretinal fluid recurred, and his vision decreased. One month after sorafenib was resumed, his vision and OCT findings improved. Case 2 showed resolution of the intraretinal fluid after sorafenib had been administered for 1 month. Neither patient developed serious adverse events. Case 1 stated that after the initial dose of sorafenib, he had mild acral dermatitis; this condition resolved spontaneously, and he continued the medication. No other adverse events were noted.

The limitations of this study are the short follow-up of the patients, the small number of treated patients, and the overlap between use of ranibizumab and sorafenib therapy. Additionally, it could be that the patients’ courses reflected the natural history of exudative AMD. However, the apparent increase in macular edema in 1 patient after discontinuation of sorafenib and the reduced macular edema after reinitiation of sorafenib in both patients suggest a monotherapeutic effect.

Kernt et al\(^9\) described a patient with renal cell carcinoma who had exudative AMD. This patient experienced improvement of his exudative AMD after use of a standard dose of sorafenib for his renal cell cancer. Although the case report by Kernt et al supports our findings, their patient received much higher doses of sorafenib than what we thought was needed for VEGFR inhibition for AMD. Adding low-dose sorafenib to standard therapy for refractory or recurrent exudative AMD, as well as trials for use as a single agent in patients with neovascular AMD, should be considered.

REFERENCES


