Predictors of AMD Treatment Response

Dear Editor:

It is important that we understand which factors dictate the visual acuity outcome in people receiving anti-vascular endothelial growth factor (anti-VEGF) for choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).[1–3] In this study, we sought to assess whether optical coherence tomography (OCT) features at baseline and after initial treatment correlated with visual outcome at 12 months. This study was approved by the Human Research and Ethics Committee of the Royal Victorian Eye and Ear Hospital.

Treatment-naïve patients diagnosed with subfoveal CNV secondary to AMD were prospectively consecutively recruited from the Medical Retina Clinic at the Royal Victorian Eye and Ear Hospital and the private rooms of the Eastern Retinal Service in Box Hill, Melbourne, Australia. All patients received 3, monthly injections of ranibizumab and/or bevacizumab, with subsequent retreatment decisions at monthly visits based on a modification of the SUSTAIN study.[4] In brief, retreatment was performed if there was either persistence or recurrence of intraretinal fluid or subretinal fluid on OCT, loss of ≥1 lines of vision, or the presence of new macular hemorrhage on clinical examination.

At baseline, OCT was assessed for the presence of an intraretinal fluid (IRF) component (cysts or edema), subretinal fluid (SRF), pigment epithelial detachment (PED), and a significant band of reflectance at the retinal pigment epithelial (RPE) level, because it has been suggested that this is a sign of irreversible damage to the outer retina/RPE.[5] After 3 injections, eyes without IRF or SRF were considered "dry," as were eyes with PED without IRF or SRF. Regardless of the presence of PED, if either IRF or SRF were present, eyes were considered as having "persistent fluid" (Fig 1A, B, available at http://aaojournal.org). The presence or absence of a hyperreflective RPE band was considered separately as it could be present irrespective of the nature of the fluid status (Fig 1C, D).

At baseline, 144 of 214 eyes (67.2%) had IRF with or without SRF and 70 (32.8%) eyes had SRF alone. Of 58 eyes (27.1%) that had PED, 38 had associated IRF, and 20 had additional SRF alone (Table 1, available at http://aaojournal.org). Best-corrected logMAR visual acuity (BCVA) at baseline was significantly worse in eyes with IRF (0.79 [Snellen equivalent, 20/122]; 95% confidence interval [CI], 0.68–0.90) compared with eyes with SRF alone (0.55 [20/72]; 95% CI, 0.34–0.75; $P = 0.006$). The presence of PED did not significantly impact on BCVA. Data at the 12-month visit were available for 187 eyes (87.4% of recruited eyes). No differences were seen with respect to the baseline population and the 187 eyes with complete data available at 12 months ($P>0.10$). Over 12 months, 26.2% of eyes gained ≥2 lines of BCVA compared with 19.3% ≥3 line gain in the SUSTAIN study.4 51.3% remained stable (±2 lines) and 22.5% lost ≥2 lines. The location of fluid at baseline did not significantly influence the likelihood of BCVA improvement at 12 months, although eyes with SRF at baseline had better BCVA (0.54 [20/69]; 95% CI, 0.34–0.75) compared with those with an IRF component (0.78 [20/120]; 95% CI, 0.63–0.93; $P = 0.07$). After the 3 initial injections, 63.1% of eyes were classified as being dry, whereas 26.2% had IRF and 10.7% had residual SRF only. The factors influencing BCVA change at 12 months are shown in Table 2 (available at http://aaojournal.org). After 3 injections, eyes that were dry had better BCVA at 12 months (0.61 [20/80]; 95% CI, 0.52–0.70) compared with those with residual IRF (0.95 [20/180]; 95% CI, 0.78–1.11; $P = 0.05$). Eyes with SRF alone (0.65 [20/90]; 95% CI, 0.39–0.91) were similar to those that were dry. The presence of persistent fluid was associated with a reduced chance of visual improvement at 12 months (18.6% vs 31.4%; $P = 0.04$).

At baseline, 6 eyes demonstrated RPE hyperreflectance. This increased to 29 (15.5%) after 3 injections. Regardless of the presence or absence of fluid, hyperreflectivity conferred a greater likelihood of BCVA loss (48.3% vs 19.7%; $P = .006$) and poorer final BCVA (0.89 [20/155]; 95% CI, 0.69–1.10) compared with eyes without hyperreflectance (0.65 [20/90]; 95% CI, 0.56–0.73; $P = 0.02$). Two thirds (66%) of eyes with PED at baseline were noted to have residual PED after initial injections with no difference in final BCVA dependent on the PED.

After 3 treatments, eyes with a residual IRF component were associated with a greater chance of BCVA loss at 12 months compared with those who were dry (odds ratio [OR], 6.08; 95% CI, 1.53–32.56; $P = 0.01$), whereas those with RPE hyperreflectivity were also more likely to lose BCVA (OR, 4.48; 95% CI, 1.11–16.41; $P = 0.03$; Tables 3 and 4, available at http://aaojournal.org). Our findings suggest that the presence of IRF fluid at baseline leads to worse presenting acuity and confers a significantly worse prognosis for visual outcome.

Failure to clear fluid from the retina after the loading dose injections also correlates with poorer BCVA outcome and with a greater chance of losing vision at month 12 (Fig 2A, B, available at http://aaojournal.org). This may relate to disruption of retinal architecture with IRF as opposed to SRF, where the retina may be relatively intact.

Failure to resolve fluid from the retina after initial treatment may be a marker of irreversible structural damage to the photoreceptor/RPE complex. Most eyes with persistent fluid after 3 injections also had persistent fluid at 12 months, suggesting that the ability to dry the retina is determined early in the course of treatment. Early in the course of treatment, RPE hyperreflectance also correlates with BCVA loss at 12 months. Most eyes with this feature had significant subretinal hemorrhage at baseline. Of the initial 214 eyes, 29 had significant hyperreflectance at the RPE level. Of these, some degree of atrophy or subretinal fibrosis was identified in 21 eyes, and of the remaining 8 eyes, 7 had residual subretinal hemorrhage, which by 12 months revealed atrophy (n = 2) or subretinal fibrosis (n = 5).

Table 5 (available at http://aaojournal.org) details findings of eyes with RPE hyperreflectance. No association was seen with presence of PED at baseline or after 3 treatments and BCVA change at 12 months. Anti-VEGF treatment however, did reduce the frequency of PED compared with baseline.

In conclusion, eyes with IRF after initial treatment may require more aggressive treatment strategies to achieve best possible outcome, whereas a significant RPE hyperreflective band limits the potential for visual improvement.

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Voriconazole for *Candida* Endophthalmitis

Dear Editor:

Endogenous fungal endophthalmitis is a serious sight-threatening complication of systemic fungemia. Infectious Diseases Society of America (IDSA) guidelines for the management of endogenous *Candida* endophthalmitis recommend intravenous amphotericin-B and oral flucytosine, possibly with vitrectomy.[1,2] Recently, there have been reports of using intravitreal voriconazole injection as a treatment option in fungal endophthalmitis, including *Aspergillus*, *Fusarium*, *Scedosporium, and Candida*. To the best of our knowledge, the following is the first reported case of combined multiple voriconazole injection and systemic medication in a patient with bilateral endogenous *Candida* endophthalmitis. We searched PubMed, MEDLINE, and Google Scholar in March 2012 for key words including bilateral endogenous fungal endophthalmitis, *Candida* endophthalmitis, drug-resistant fungal endophthalmitis, and multiple intravitreal voriconazole injection (all languages without dates restriction), which showed no prior reports of bilateral *Candida* endophthalmitis successfully treated with multiple intravitreal voriconazole injections combined with systemic medication.

A 69-year-old man with diabetic mellitus, was referred to our emergency room due to pain and blurring vision in both eyes for 2 weeks. He had undergone right percutaneous nephrolithotomy 1 month ago at another hospital, complicated with subsequent *Candida* urosepsis. Urine culture showed *Candida albicans*. Then days later, he undergone cholecystectomy due to cholecystitis, but further blood culture revealed *Candida albicans*. Following this, intravenous fluconazole was prescribed for 9 days. Fundus examination revealed multifocal yellow-white lesions with fluffy borders, severe vitritis with "string-of-pearls" signs in both eyes, compatible with the diagnosis of *Candida* endophthalmitis (Fig 1A–B; available at http://aaojournal.org). Visual acuity was counting fingers only in both eyes. There was anterior chamber flare++ and cells++. Optical coherence tomography (OCT) showed multiple chorioretinal lesions with marked retinal thickening, protrusion, and poor macular contour (Fig 2A–B; available at http://aaojournal.org).

In addition to systemic therapy with amphotericin-B and flucytosine, the patient was treated with intravitreal voriconazole injection (100 μg/0.1 ml) immediately, again at the time of vitrectomy in both eyes 3 days later after systemic condition stabilized, and further weekly intravitreal injection. After 6 weeks of treatment, retinal lesions showed regression, and visual acuity improved from counting fingers to 1/60 in right eye and 6/60 in left eye. Fundus examination (Fig 3A–B available at http://aaojournal.org) and OCT (Fig 4A–B; available at http://aaojournal.org) 4 months after treatment demonstrated significant improvement of the endophthalmitis with resolution of *candida* chorioretinitis and subretinal chorioretinal scarring. Later cultures of blood, urine, and vitreous were negative for fungus growth. Latest ocular examination reported stable visual acuity.

Voriconazole, a promising broad-spectrum triazole agent, solves difficult cases as failure in first-line treatment or drug-resistant fungus. For vision-threatening macular involvement, intravitreal voriconazole injection is an effective way for rapid achievement of therapeutic concentration with minimal systemic side effect. Instead of single injection, the current case was treated with multiple injections during the treatment course. In a study regarding the clearance profile of intravitreal voriconazole, injecting 35 μg/0.1 mL into vitreous cavity of rabbit yielded a fast decline of concentration, with half-life of 2.5 hours and rapid decay within 24 hours after injection.[3] The authors suggest that supplementation of intraocular voriconazole to maintain therapeutic levels might be required.[3] An in vitro safety study claimed that concentrations $<$250 μg/mL of voriconazole had no influence neither on human retinal pigmented epithelium nor on optic nerve head astrocytes cell proliferation and cell viability.[4] In our case, the estimated concentration after injecting voriconazole 100 μg/0.1 ml into vitreous cavity (which became 2.5 μg/ml in a 4 ml-volume vitreous cavity) doesn't exceed the safety range.

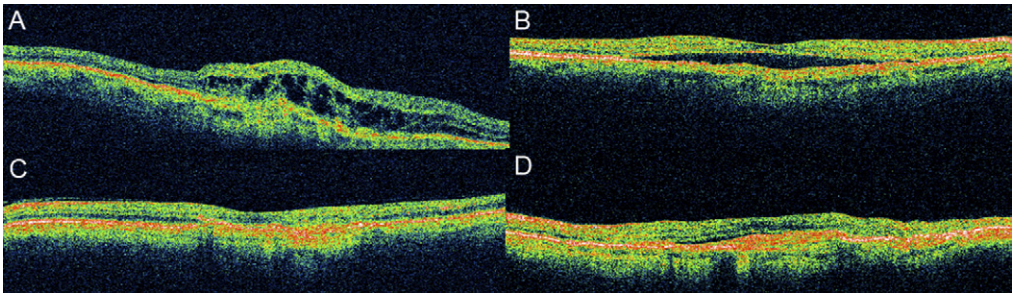


Figure 1. A, Optical coherence tomography scans depicting intraretinal fluid (IRF), (**B**) subretinal fluid (SRF), and a hyperreflective retinal pigment epithelial (RPE) band, with (**C**) or without (**D**) fluid.

Table 1. Background and Treatment Characteristics of 214 Eyes Included in the Study

Characteristic	n	%
Age group (yrs)		
<75	43	20.1
75–84	124	57.9
≥85	47	22.0
Gender		
Male	83	38.8
Female	131	61.2
Smoking status, if known		
Never smoker	81	42.2
Smoker (past or present)	111	57.8
Type of CNV lesion		
Predominantly classic	54	25.2
Nonpredominantly classic*	160	74.8
Size of CNV (DA)		
≥2	136	63.5
>2	78	36.5
Baseline OCT appearance		
IRF with SRF	144	67.2
SRF	70	32.8
Hyperreflectivity of RPE	6	2.8
Treatment type		
Ranibizumab and bevacizumab combination	72	33.6
Ranibizumab	142	66.4
Delay in seeking treatment, median weeks (IQR)	12.0 (5.0–26.0)	
Baseline BCVA, median (IQR)	0.60 (0.42–0.86)	
No. of injections at 12 months, median (IQR)	5 (3–7)	

BCVA = best-corrected logMAR visual acuity; CNV = choroidal neovascularization; DA = disc areas; IQR = interquartile range; IRF = intraretinal fluid; OCT = optical coherence tomography; RPE = retinal pigment epithelium; SRF = subretinal fluid.
*Includes minimally classic, occult, retinal angiomatous proliferation, fibrovascular RPE detachment.

Table 2. Visual Outcome at 12 Months Based on Baseline and Treatment Characteristics of Study Eyes

Characteristic	Change in BCVA at 12 Months			P Value
	Improved BCVA (>2 Line Gain; n = 49; 26.2%)	*Stable BCVA (≤2 Line Gain or Loss; n = 96; 51.3%)*	*Decreased BCVA (>2 Line Loss; n = 42; 22.5%)*	
Age group, n (%), yrs				0.37†
<75	14 (35.9)	18 (46.2)	7 (17.9)	
75–84	26 (24.5)	58 (54.7)	22 (20.8)	
≥85	9 (21.4)	20 (47.6)	13 (31.0)	
Gender, n (%)				0.01†
Male	23 (31.9)	27 (37.5)	22 (30.6)	
Female	26 (22.6)	69 (60.0)	20 (17.4)	
Smoking status if known, n (%)				0.38†
Never smoker	22 (31.9	34 (49.3)	13 (18.8)	
Smoker (past or present)	23 (23.0)	52 (52.0)	25 (25.0)	
Type of CNV lesion, n (%)				0.13†
Predominantly classic	18 (36.7)	20 (51.3)	11 (22.4)	
Nonpredominantly classic*	31 (22.5)	76 (55.1)	31 (22.5)	
Size of CNV, n (%), DA				0.44†
≤2	34 (29.0)	59 (50.4)	24 (20.5)	
>2	16 (22.8)	35 (50.0)	19 (27.2)	
Delay in seeking treatment (weeks), median (IQR)	11.5 (4.0–31.0)	12.0 (4.5–26.0)	12.0 (6.5–21.5)	0.06‡
Baseline BCVA, median (IQR)	0.69 (0.48–1.00)	0.60 (0.33–0.78)	0.60 (0.48–0.78)	0.22‡
OCT appearance at baseline, n (%)				
IRF with or without SRF	42 (29.2)	66 (45.8)	36 (25.0)	0.49†
SRF	22 (31.4)	38 (54.2)	10 (14.2)	
Hyperreflectivity of RPE	1 (17.0)	3 (50.0)	2 (33.0)	0.54†
Pigment epithelial detachment	11 (19.0)	27 (47.6)	20 (32.4)	0.26†
Treatment type				
Ranibizumab/bevacizumab combination	16 (23.5)	36 (52.9)	16 (23.5)	0.74†
Ranibizumab	34 (28.6)	60 (50.4)	25 (21.0)	
No. of injections at 12 months, median (IQR)	6 (4–8)	5 (4–7)	4 (3–5)	0.01‡
Residual fluid on OCT at 3 months, n (%)				
No residual fluid/dry	37 (31.4)	59 (50.0)	22 (18.6)	
IRF with or without SRF	9 (18.4)	22 (44.9)	18 (36.7)	0.15†
SRF	4 (20.0)	9 (45.0)	7 (35.0)	
Pigment epithelial detachment on OCT at 3 months, n (%)				
Yes	10 (25.8)	17 (45.2)	11 (29.0)	0.85†
No	40 (26.7)	73 (49.2)	36 (24.2)	
RPE hyperreflectance on OCT at 3 months, n (%)				
Hyperreflectivity of RPE	5 (17.2)	10 (34.5)	14 (48.3)	
No hyperreflectivity	45 (28.7)	82 (51.6)	31 (19.7)	0.006†

BCVA = best-corrected LogMAR visual acuity; CNV = choroidal neovascularization; DA = disc areas; OCT = optical coherence tomography; IQR = interquartile range; IRF = intraretinal fluid; RPE = retinal pigment epithelium; SRF = subretinal fluid.
*Includes minimally classic, occult, retinal angiomatous proliferation, fibrovascular RPE detachment.
†Chi square test.
‡Analysis of variance test.

Table 3. Results of Generalized Estimating Equations Modeling of the Effects of Patient and Treatment Characteristics on Visual Acuity Outcomes at 12 Months

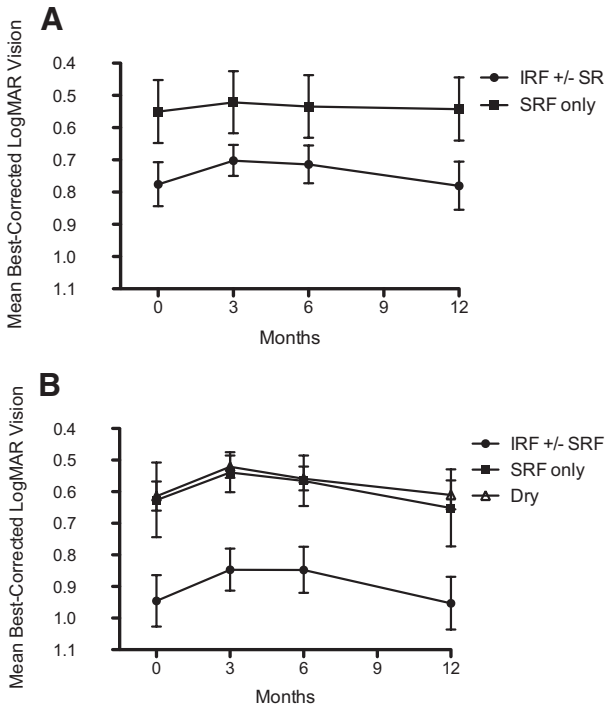
Predictor	Improved vs Stable BCVA*			Improved vs Decreased BCVA*		
	OR	*95% CI*	*P Value*	*OR*	*95% CI*	*P Value*
OCT appearance						
No residual fluid (dry)	1.00	Reference		1.00	Reference	
IRF with or without SRF	1.93	0.56–6.30	0.27	6.08	1.53–24.14	0.01
SRF	1.62	0.36–7.30	0.53	4.31	0.40–46.92	0.23
Male gender	1.86	0.72–4.80	0.20	0.52	0.16–1.72	0.28
No. of injections	0.87	0.70–1.07	0.19	0.67	0.50–0.88	0.004
Delay in treatment	0.98	0.96–1.00	0.15	0.97	0.95–1.02	0.06

BCVA = best-corrected LogMAR visual acuity; CI = confidence interval; IRF = intraretinal fluid; OCT = optical coherence tomography; OR = odds ratio; SRF = subretinal fluid.
*Reference group is improved VA.

Table 4. Results of Generalized Estimating Equations Modeling of the Effects of Patient and Treatment Characteristics on Visual Acuity Outcome at 12 Months

Predictor	Improved vs. Stable BCVA*			Improved vs. Decreased BCVA*		
	OR	*95% CI*	*P-Value*	*OR*	*95% CI*	*P-Value*
OCT appearance						
No hyperreflectivity of RPE	1.00	Reference		1.00	Reference	
Hyperreflectivity of RPE	1.32	0.26–6.66	0.74	4.48	1.11–16.41	0.03
Male gender	1.60	0.62–4.13	0.33	0.44	0.14–1.39	0.16
Number of injections	0.85	0.69–1.04	0.12	0.74	0.56–0.98	0.03
Delay in treatment	0.99	0.96–1.01	0.20	0.97	0.95–1.02	0.06

BCVA = best-corrected logMAR visual acuity; OR = odds ratio; CI = confidence interval; SRF = subretinal fluid; IRF = intraretinal fluid.
*Reference group is improved VA.



IRF, intrareinal fluid; SRF, subretinal fluid

Error bars represent the standard error of the mean LogMAR visual acuity

Figure 2. A, Change in mean visual acuity over time, depending on location of fluid within the macula on optical coherence tomography. **B**, Change in mean visual acuity over time, depending on presence and location of fluid within the macula on optical coherence tomography after 3 antivascular growth factor treatments.

Table 5. Clinical Features of Patients with a Band of Hyperreflectivity at the Level of the Retinal Pigment Epithelium (RPE) on Optical Coherence Tomography (OCT) after 3 Antivascular Endothelial Growth Factor Treatments

	Clinical Appearance			
OCT Appearances	*Fibrosis*	*Atrophy*	*Chronic PED*	*Subretinal Hemorrhage*
Hyperreflectivity with residual fluid (n = 14)	8	1	0	5
Hyperreflectivity with no residual fluid (n = 15)	4	8	1	2

atrophy = window defect in early phase of angiogram with loss of retinal pigment epithelium clinically; fibrosis = >25% of lesion is fibrotic scar; PED = retinal pigment epithelial detachment; subretinal hemorrhage = large subfoveal hemorrhage with significant masking of details on angiography.