was 13.8 letters. This is comparable with recent but smaller studies of ranibizumab therapy in myopic CNV.[2–4] Encouraging improvements in patient-reported outcome measures were also found and retreatment rates were low.

One limitation of the study was the lack of a reading center. Observer variation may explain the high frequency of subretinal fluid graded by individual investigators at baseline. Alternatively, the high rate may represent misclassification, because it has previously been shown that human graders are good at agreeing whether fluid is present or absent, but are poor at distinguishing subretinal from intraretinal fluid.[5] Because any fluid present on OCT would drive retreatment, misclassification would not affect the decision to treat.[5] However, possible grading inconsistencies should not affect our main conclusion regarding the primary visual outcome and the quantitative anatomic outcomes. The other limitation was the lack of a control arm. Both of these limitations should be better addressed in future comparative trials such as the phase III RADIANCE study comparing ranibizumab with verteporfin-PDT (clinicaltrials.gov identifier NCT01217944). Currently, this report provides a useful evidence to support the use of primary ranibizumab therapy in treatment-naïve myopic CNV, gives an estimate of the likely burden of treatment, and provides a pragmatic retreatment algorithm, that is easily translated into clinical practice.

Adnan Tufail, MD, FRCOphth[1]
Nirodhini Narendran, MD, FRCOphth[2]
Praveen J. Patel, MBBS, FRCOphth, MD(Res)[1]
Sobha Sivaprasad, DM, FRCS[1]
Winfried Amoaku, MBBS, FRCOphth[3]
Andrew C. Browning, BM, FRCOphth[4]
Olayinka Osoba, MBBS, FRCS(Ed)[5]
Richard Gale, MBBS, MRCP, MRCOphth[6]
Sheena George, MBBS, FRCOphth[7]
Andrew J. Lotery, MD, FRCOphth[8]
Mohammed Majid, MBBS, FRCOphth[9]
Martin McKibbin, MBBS, FRCOphth[10]
Geeta Menon, MBBS, FRCOphth[11]
Christopher Andrews, CStat[12]
Christopher Brittain, MBBS, MRCOphth[12]
Aaron Osborne, MBBS, MRCOphth[12]
Yit Yang, MBChB, FRCOphth[2]

[1]*NIHR Moorfields Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation, Trust and UCL Institute of Ophthalmology, London, UK;* [2]*Wolverhampton Eye Infirmary, Wolverhampton, UK;* [3]*University of Nottingham, Queens Medical Centre, Nottingham, UK;* [4]*Newcastle Eye Centre, Royal Victoria Infirmary, Newcastle, UK;* [5]*Torbay Hospital, Torquay, UK;* [6]*York Teaching Hospital, York, UK;* [7]*Western Eye Hospital, London, UK;* [8]*Clinical Neurosciences and Experimental Sciences, Faculty of Medicine Division, University of Southampton, Southampton, UK;* [9]*Bristol Eye Hospital, Bristol, UK;* [10]*St James's University Hospital, Leeds, UK;* [11]*Frimley Park Hospital NHS Foundation Trust, Frimley, UK;* [12]*Novartis Pharmaceuticals Ltd., Surrey, UK*

Financial Disclosures: Novartis Pharmaceuticals UK Ltd., Surrey, UK participated in the design and conducting of the study; data collection, management, analysis, and interpretation; and preparation and review of the manuscript.

References

1. Tufail A, Patel PJ, Sivaprasad S, et al. Ranibizumab for the treatment of choroidal neovascularisation secondary to pathological myopia: interim analysis of the REPAIR study. Eye (Lond) 2013;27:1–7.
2. Lai TY, Luk FO, Lee GK, Lam DS. Long-term outcome of intravitreal anti-vascular endothelial growth factor therapy with bevacizumab or ranibizumab as primary treatment for subfoveal myopic choroidal neovascularization. Eye (Lond) 2012;26:1004–11.
3. Wu TT, Kung YH. The 12-month outcome of three consecutive monthly intravitreal injections of ranibizumab for myopic choroidal neovascularization. J Ocul Pharmacol Ther 2012;28:129–33.
4. Franqueira N, Cachulo ML, Pires I, et al. Long-term follow-up of myopic choroidal neovascularization treated with ranibizumab. Ophthalmologica 2012;227:39–44.
5. Patel PJ, Browning AC, Chen FK, et al. Interobserver agreement for the detection of optical coherence tomography features of neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci 2009;50:5405–10.

Two Year SAVE Outcomes: 2.0 mg Ranibizumab for Recalcitrant Neovascular AMD

The *S*uper-dose *A*nti-*VE*GF (SAVE) trial assessed the efficacy of 2.0 mg ranibizumab (0.05 ml), a 4-fold higher dose than the 0.5 mg dose approved by the US Food and Drug Administration, for the management of recalcitrant neovascular age-related macular degeneration (AMD) in 88 patients.[1,2] Primary outcome results of the 3-month, fixed-interval dosing period were reported in *Ophthalmology*, and in this report we offer 2-year follow-up data.

Recalcitrant fluid despite monthly or near-monthly anti-vascular endothelial growth factor (VEGF) therapy is a common clinical scenario in the management of neovascular AMD. Indeed, more than one half of patients treated with anti-VEGF agents in prospective neovascular AMD trials manifest residual intraretinal, subretinal, or subretinal pigment epithelium fluid despite maximal anti-VEGF dosing.[3] This persistent macular edema likely limits maximal visual recovery in these challenging cases.[4]

Higher dose of existing anti-VEGF agents, as assessed prospectively in SAVE, is a potential route for managing these incomplete responders. At study entry, patients had received an average of 24 previous intravitreal injections of anti-VEGF agents, including monthly dosing in the year before enrollment (mean time between injections of 31 days). After 3 monthly 2.0 mg doses, patients were evaluated every 4 weeks (cohort A) or every 6 weeks (cohort B) and retreated as needed (PRN) for any intraretinal, subretinal, or subretinal pigment epithelium fluid detected on spectral domain optical coherence tomography (SD OCT).

After 3 monthly treatments, mean Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) improved +3.3 letters ($P = 0.001$) and mean SD OCT central retinal subfield thickness (CST) improved −33.1 μm ($P = 0.01$).[1] Visual gains were maintained through month 12,[2] with cohorts A and B gaining a mean of +4.1 and +3.7 ETDRS letters, respectively, after receiving a mean of 11.6 (cohort A) and 8.6 (cohort B) injections.[2] Anatomically, monthly PRN retreatment led to continued retinal detergescence through year 1, whereas every 6 week PRN

retreatment led to a significant, gradual increase in mean CST ($P = 0.03$).

Therefore, for the second year of the SAVE trial, the protocol was modified: Both cohorts were evaluated monthly with PRN retreatment. Of the 79 patients who completed 1 year, 77 completed 20 months and 64 completed 24 months (cohort A, n = 33; cohort B, n = 31). Patient attrition was precipitated by cessation of production of 2.0 mg ranibizumab after release of the HARBOR trial results.[3]

During the second year of the SAVE trial, mean PRN retreatments were 11.2 (range, 5−12) and 11 (range, 6−12) for cohorts A and B, respectively. Highlighting the recalcitrant nature of the choroidal neovascular complexes in these patients, a majority of patients, 25/33 (76%) and 19/31 (61%) of cohorts A and B, respectively, received all possible PRN injections. Upon switching cohort B from PRN retreatment every 6 weeks to every 4 weeks, mean SD OCT CST decreased to a comparable level as had been observed in cohort A (Fig 1; available at http://aaojournal.org); at month 24, CST was −73 and −66 μm for cohorts A and B, respectively. During the second year, mean ETDRS BCVA gains remained stable and similar between cohorts (Fig 2; available at http://aaojournal.org); at month 24, BCVA gains were +3.6 and +2.9 letters for cohorts A and B, respectively. The ocular and systemic safety of 2.0 mg intravitreal ranibizumab observed in SAVE was consistent with previous trials of ranibizumab including the 2.0 mg cohort in HARBOR.[3]

Other trials have also assessed the potential role of higher doses of anti-VEGF medications in AMD management. The phase III HARBOR trial found no difference in visual or anatomic outcomes in patients randomized to 2.0 versus 0.5 mg ranibizumab.[3] Critically, however, HARBOR included only treatment-naïve neovascular AMD eyes. Supporting the concept that a higher dose of anti-VEGF medication may be more valuable in neovascular AMD patients with an incomplete anatomic response to conventional therapy, Fung et al[5] reported a group of 7 recalcitrant neovascular AMD eyes treated with 2.0 mg ranibizumab who experienced visual gain and anatomic improvement.

The burden of neovascular AMD eyes with recalcitrant fluid despite adequate anti-VEGF therapy is a common clinical challenge. Many alternative treatment approaches have been considered and continue to be investigated, such as radiation therapy and extended-release formulations and devices, as well as pharmaceuticals directed at alternative molecular targets. As a part of this multidimensional approach to delivering optimal visual benefit, a higher dose of ranibizumab merits further study as a management tool for patients with recalcitrant neovascular AMD.

Charles C. Wykoff, MD, PhD
David M. Brown, MD
Daniel E. Croft, BA
Tien P. Wong, MD

Retina Consultants of Houston, The Methodist Hospital, Houston, Texas

Financial Support: Research grant from Genentech. The funding organization had no role in the design or conduct of this research. SAVE Trial: IND 12246, NCT 00406471 http://clinicaltrials.gov/show/NCT00406471.

References

1. Brown DM, Chen E, Mariani A, et al; SAVE Study Group. Super-dose anti-VEGF (SAVE) trial: 2.0 mg intravitreal ranibizumab for recalcitrant neovascular macular degeneration-primary end point. Ophthalmology 2013;120:349–54.
2. Wykoff CC, Brown DM, Chen E, et al. SAVE (Super-dose Anti-VEGF) trial: 2.0 mg ranibizumab for recalcitrant neovascular age-related macular degeneration: 1-year results. Ophthalmic Surg Lasers Imaging Retina 2013;44:121–6.
3. Busbee BG, Ho AC, Brown DM, et al; Harbor Study Group. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology 2013;120:1046–56.
4. Brown DM, Tuomi L, Shapiro H, PIER Study Group. Anatomical measures as predictors of visual outcomes in ranibizumab-treated eyes with neovascular age-related macular degeneration. Retina 2013;33:23–34.
5. Fung AT, Kumar N, Vance SK, et al. Pilot study to evaluate the role of high-dose ranibizumab 2.0 mg in the management of neovascular age-related macular degeneration in patients with persistent/recurrent macular fluid <30 days following treatment with intravitreal anti-VEGF therapy (the LAST Study). Eye (Lond) 2012;26:1181–7.

Headache or Eye Pain as the Presenting Feature of Uveal Melanoma

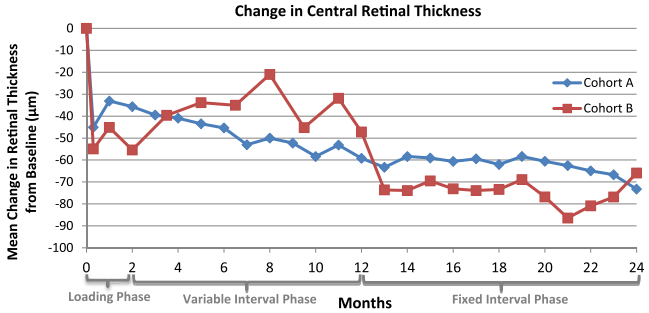
Uveal melanoma classically presents as a painless intraocular mass.[1] Related features such as retinal detachment, vitreous hemorrhage, or extraocular extension, typically do not generate pain. Pain is rare, found in <1% of cases, and can be caused by severely elevated intraocular pressure from neovascular or angle-closure glaucoma,[2] or it can result from spontaneous tumor necrosis.[3] Often there is delay in diagnosis as the headache or ocular pain is attributed to sinusitis, dental infection, muscle or emotional stress, or migraine etiology.

There have been a few reports that have addressed the association of ocular pain with uveal melanoma. Herein, we describe our experience with 15 patients who presented with headache or ocular pain and were subsequently discovered to have an underlying uveal melanoma. The medical records of 15 patients with uveal melanoma who presented with pain and examined on the Ocular Oncology Service, Wills Eye Institute, Philadelphia, Pennsylvania, were reviewed. Of approximately 4940 patients with uveal melanoma examined between July 2003 and December 2012, every patient had a detailed history and occurrence of pain was recorded. Fifteen patients were found to have presented with pain. Institutional review board approval was obtained for this study. The study and data collection conformed to local laws and were compliant with the principles of the Declaration of Helsinki.

History of ocular trauma, previous uveitis, glaucoma, migraine, or autoimmune disease was ruled out. The headache or ocular pain was assessed for severity based on subjective pain rating on a scale of 0 to 10 (from 0 [no pain] to 10 [worst pain]), pain location, duration, and treatment.

The ophthalmic findings included best-corrected visual acuity, anterior segment findings by slit-lamp biomicroscopy and gonioscopy, intraocular pressure measurement, and fundus findings by indirect ophthalmoscopy. Melanoma features included tumor size, location, and configuration. Surrounding tissue features included anterior or posterior uveitis, status of the vitreous, retina, choroid, and sclera.

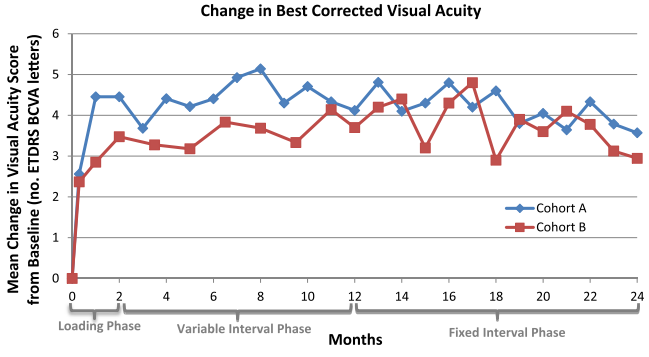
Data regarding ocular imaging included features on globe transillumination, optical coherence tomography, fundus photography, and ultrasonography. Additional imaging with computed tomography or magnetic resonance imaging was performed when



Mean (±SE) Change in Central Retinal Thickness from Baseline (µm)

Cohort	Month 2	Month 6	Month 12	Month 24
A	-35.7 ±7.4	-45.3 ±9.0	-59.2 ±16.1	-73.2 ±21.2
B	-55.4 ±12.2	-35.0 ±16.0	-47.2 ±12.5	-65.9 ±20.0

Figure 1. Change in mean central retinal subfield thickness (spectral domain optical coherence tomography) in cohorts A and B over 24 months. Three phases are depicted. During the loading phase, both cohorts received monthly treatment. During the variable interval phase, cohort A received monthly visits with as-needed (PRN) retreatment and cohort B received visits and PRN retreatment every 6 weeks. During the fixed interval phase, all patients received monthly visits and PRN retreatment and missing data were imputed by last observation carried forward.



Mean (±SE) Change in Best Corrected Visual Acuity from Baseline (no. of Letters)

Cohort	Month 2	Month 6	Month 12	Month 24
A	+4.5 ±1.0	+4.4 ±0.9	+4.1 ±1.4	+3.6 ±1.8
B	+3.5 ±0.8	+3.8 ±1.0	+3.7 ±1.0	+2.9 ±1.3

Figure 2. Change in mean best-corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study letters) in cohorts A and B over 24 months. Three phases are depicted. During the loading phase, both cohorts received monthly treatment. During the variable interval phase, cohort A received monthly visits with as-needed (PRN) retreatment and cohort B received visits and PRN retreatment every 6 weeks. During the fixed interval phase, all patients received monthly visits and PRN retreatment and missing data were imputed by last observation carried forward.