Graefes Arch Clin Exp Ophthalmol (2007) 245:1877–1880
DOI 10.1007/s00417-007-0679-1

CASE REPORT

Ranibizumab for retinal angiomatous proliferation in neovascular age-related macular degeneration

Timothy Y. Y. Lai · Wai-Man Chan · David T. Liu · Dennis S. Lam

Received: 25 June 2007 / Revised: 11 August 2007 / Accepted: 27 August 2007 / Published online: 28 September 2007

Abstract
Background To report the efficacy of intravitreal injection of ranibizumab (Lucentis) in the treatment of retinal angiomatous proliferation (RAP) in neovascular age-related macular degeneration (AMD).
Methods Case review of four consecutive patients who received 3 injections at monthly intervals of intravitreal ranibizumab injections for RAP. The serial changes in best-corrected visual acuity (BCVA), optical coherence tomography (OCT), fluorescein angiography (FA), and indocyanine green angiography (ICGA) are presented.
Results The baseline mean logMAR BCVA was 0.89 (Snellen equivalent of 20/155). After three injections of ranibizumab, all four patients had visual improvement and the mean logMAR BCVA improved to 0.59 (Snellen equivalent of 20/78). The mean visual improvement was 3.0 lines. All patients also had complete resolution of subretinal fluid after treatment, and the mean OCT central foveal thickness reduced from 438 μm at baseline to 169 μm at 3 months. Follow-up FA and ICGA at 3 months showed absence of leakage in three patients with minimal leakage in the remaining patient. One patient had recurrence of RAP at 8 months after commencement of treatment, and repeat ranibizumab injection resulted in resolution of the subretinal fluid and pigment epithelial detachment and visual improvement.
Conclusions Intravitreal ranibizumab injections appeared to be an effective treatment for RAP, resulting in visual gain and reduction in macular thickness. Further long-term studies to evaluate the efficacy of intravitreal ranibizumab in RAP are warranted.

Keywords Retinal angiomatous proliferation · Age-related macular degeneration · Ranibizumab · Anti-VEGF

T. Y. Y. Lai (✉) · W.-M. Chan · D. T. Liu · D. S. Lam
Department of Ophthalmology and Visual Sciences,
The Chinese University of Hong Kong, Hong Kong Eye Hospital,
147K Argyle Street,
Hong Kong, SAR, People's Republic of China
e-mail: tyylai@cuhk.edu.hk

Introduction

Retinal angiomatous proliferation (RAP) is a distinctive form of neovascular age-related macular degeneration (AMD) in which new vessels originate from the middle and inner retina instead of arising from the choroidal circulation as in choroidal neovascularization [4, 10]. These neovascularizations may eventually grow into the choroidal layer, forming retinal–choroidal anastomosis [10]. The treatment outcomes of AMD patients with RAP lesions are generally less favourable than for those without RAP lesions [1]. Various treatment modalities including direct laser photocoagulation, surgical removal, and photodynamic therapy (PDT) with verteporfin (with or without intravitreal triamcinolone) have been used in the treatment of RAP [1, 2, 6]. However, the results were discouraging as most patients still developed visual loss despite treatment [1, 2, 6]. More recently, intravitreal administration of anti-vascular endothelial growth factor (VEGF) agents such as bevacizumab has also been used for treating RAP, and the results appeared favourable [7, 8]. We hereby report the outcomes of four patients who received intravitreal ranibizumab injections for RAP.

Material and methods

Four patients who received intravitreal ranibizumab injections for the treatment of RAP at the Department of

Ophthalmology & Visual Sciences, The Chinese University of Hong Kong were retrospectively reviewed. Diagnosis of RAP was made based on fundus examination, fluorescein angiography (FA) and indocyanine green angiography (ICGA) findings, and classified according to the classification by Yannuzzi et al. [4, 10]. Best-corrected visual acuity (BCVA) was assessed using logMAR chart at 4 m, and optical coherence tomography (OCT) was performed using the Stratus OCT (Carl Zeiss Meditec, Dublin, CA, USA) and the central foveal thickness (CFT) was measured using the retinal thickness mode at the fovea. After informed consent was obtained, all patients underwent three intravitreal injections of 0.05 ml of 0.5 mg ranibizumab (Lucentis, Novartis, Switzerland) at baseline, 1 and 2 months. Injection of ranibizumab was performed as an out-patient procedure under topical anaesthesia with strict aseptic technique at 4 mm posterior to the limbus. Patients were given topical levofloxacin (Cravit, Santen, Osaka, Japan) antibiotic eye drops qid for 1 week after each injection. BCVA and OCT assessments were performed at monthly intervals, and repeat FA and ICGA were performed at 3 months to assess the treatment outcome. Retreatment was planned for cases with persistent leakage on FA or ICGA or residual subretinal fluid on OCT.

Results

The demographics data and the serial changes in logMAR BCVA and OCT CFT of the patients are listed in Table 1. The mean age of the patients was 81.0 years, and patients were followed for 5 to 10 months. None of the patients had received any previous treatment for RAP. At baseline, the mean logMAR BCVA was 0.89 (Snellen equivalent of 20/155). After a single injection of ranibizumab, the mean logMAR BCVA improved to 0.74 (Snellen equivalent of 20/110). At 3 months, the mean logMAR BCVA further improved to 0.59 (Snellen equivalent of 20/78). The mean lines of BCVA improvement at 3 months was 3.0 lines.

For the macular thickness, the mean OCT CFT at baseline was 438 μm. All four patients had marked reduction in subretinal fluid at 1 month following the first intravitreal ranibizumab injection, and the mean OCT CFT reduced to 193 μm at 1 month. Pigment epithelial detachments (PED) were present in two patients at baseline, and there was complete resolution of the PED after the first intravitreal ranibizumab injection. At 3 months, all patients had complete absence of subretinal fluid, and the mean OCT CFT reduced to 169 μm.

FA and ICGA performed at 3 months showed absence of angiographic leakage in three patients, and one patient (no. 4) had minimal persistent leakage in FA. She requested a second course of three ranibizumab injections to prevent potential worsening of the vision, and additional treatments

Table 1 Demographics data and changes in logMAR best-corrected visual acuity and central foveal thickness of the four patients who received intravitreal ranibizumab for retinal angiomatous proliferations

Patient No	Gender / Age	RAP Stage*	Follow-up duration (months)	Number of ranibizumab injections	Best-corrected visual acuity (logMAR unit)				Central foveal thickness (μm)			
					Baseline	Month 1	Month 2	Month 3	Final	Baseline	Month 1	Month 2	Month 3	Final
1	F / 74	3 with PED	10	5	0.40	0.10	0.06	0.06	0.22	471	161	150	149	144
2	F / 84	2	6	3	1.28	1.12	1.14	1.00	0.98	392	185	132	132	139
3	M / 84	2 with PED	6	3	0.48	0.32	0.32	0.30	0.30	411	135	138	130	135
4	F / 82	2	5	5	1.40	1.40	1.24	1.00	1.00	478	290	282	265	180

RAP = retinal angiomatous proliferation; PED = pigment epithelial detachment
*RAP staging was classified according to Yannuzzi et al. [10]. Stage 1 is defined as RAP with intraretinal neovascularization, stage 2 as subretinal neovascularization, and stage 3 as RAP with choroidal neovascularization.

resulted in further reduction in CFT and stable vision. Another patient (no. 1) had recurrence of RAP at 8 months with PED and subretinal fluid accumulation, and the logMAR BCVA reduced to 0.40. She underwent further ranibizumab injection, which resulted in BCVA improvement to 0.24 and complete regression of the PED and subretinal fluid 1 month after retreatment. None of the patients developed any ocular including retinal pigment epithelial atrophy and systemic complications associated with ranibizumab injections. An example of the changes in FA and OCT findings is displayed in Fig. 1.

Discussion

Despite two large-scale randomized controlled trials, ANCHOR and MARINA, demonstrating that ranibizumab is effective in the treatment of neovascular AMD [3, 9], it was uncertain whether ranibizumab is effective in the treatment of neovascular AMD with RAP lesions due to its poorer natural history. Based on the results in the use of intravitreal bevacizumab for RAP [7, 8], ranibizumab should also be effective for RAP lesions, since both drugs are potent anti-VEGF agents and increased VEGF expres-

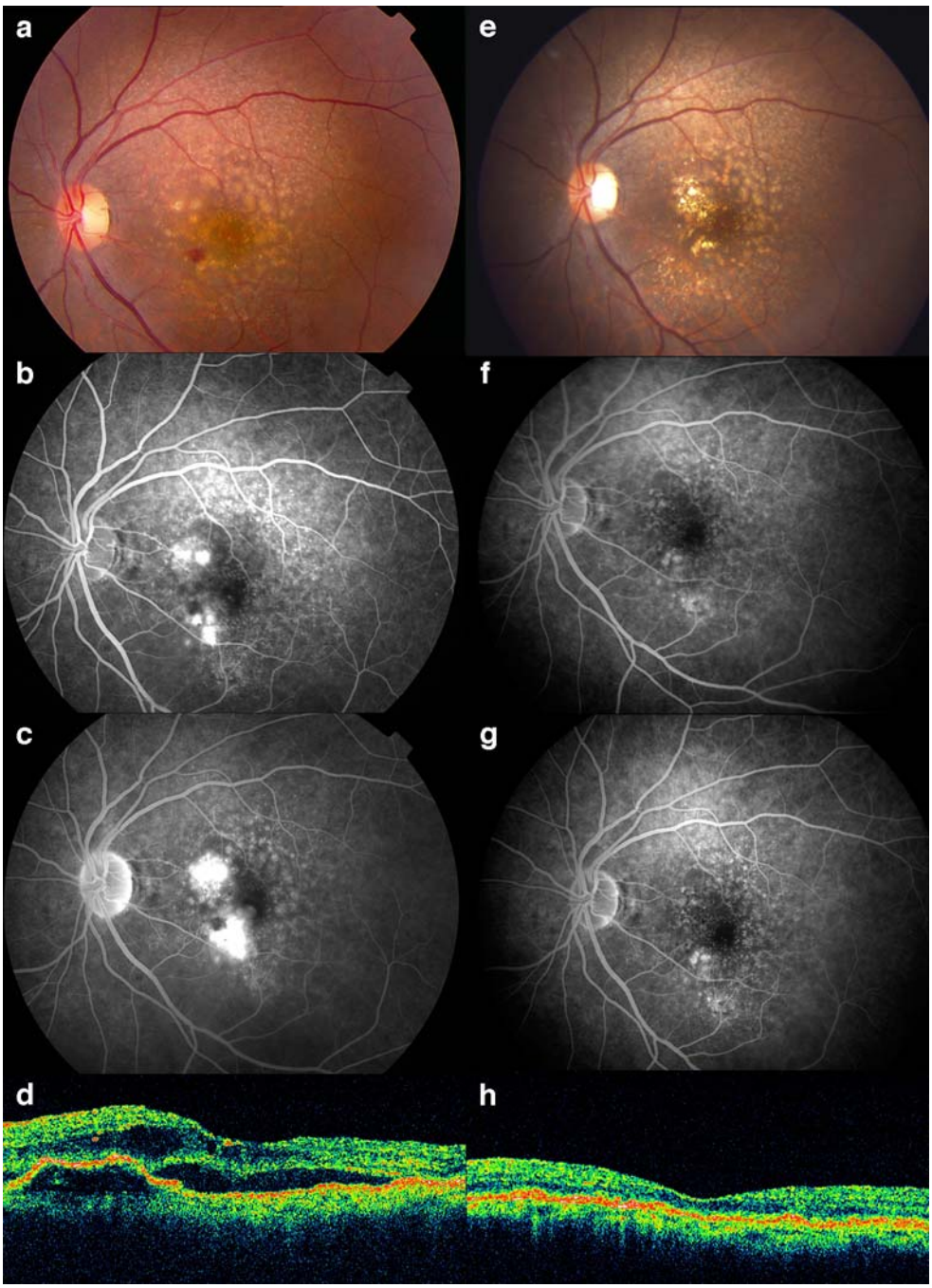

Fig. 1 **a** Left eye fundus photo, (**b**) early and (**c**) late phase fluorescein angiography of patient no. 1 prior to ranibizumab treatment demonstrating two retinal angiomatous proliferation (RAP) lesions with active leakage. **d** Optical coherence tomography (OCT) at baseline, showing subretinal fluid with adjacent pigment epithelial detachment. The patient's logMAR visual acuity was 0.4 (20/50). **e** Fundus photo, (**f**) early and (**g**) late phase fluorescein angiography of the patient 1 month after the third ranibizumab injection, showing absence of leakage with regression of the RAP lesions. **h** OCT showed complete resolution of the pigment epithelial detachment and subretinal fluid. The patient's logMAR visual acuity improved to 0.06 (20/23)

sion has been implicated as a cause of RAP [10]. In the PrONTO study [5], Fung et al. reported that ten of the 40 patients had RAP lesions, and they required a higher mean number of ranibizumab treatments compared with patients with non-RAP lesions. However, the visual acuity and OCT outcomes of patients with RAP lesions were not reported separately, and therefore it remained unclear how effective ranibizumab was in the treatment of RAP.

As demonstrated in our small case series, all four patients had BCVA improvement as well as resolution of subretinal fluid on OCT examination following ranibizumab injections. These findings are consistent with previous studies using bevacizumab for RAP which resulted in significant visual improvement and reduction in central macular thickness following treatment [7, 8]. The results in the use of anti-VEGF therapy for RAP lesions are encouraging, since other treatment modalities were unable to achieve such an extent of visual gain. In addition, PDT with verteporfin might potentially result in visual loss due to retinal damage caused by intraretinal activation of the photosensitizing drug [6, 10]. Therefore, anti-VEGF therapy might be the treatment of choice in RAP.

One patient in our series developed recurrence of RAP at 8 months after commencement of treatment, and the patient responded well to ranibizumab retreatment. Due to the short duration of follow-up, it remained uncertain whether additional ranibizumab treatments are required in other patients due to recurrence of the RAP lesions. Nonetheless, based on the encouraging results observed in our cases, ranibizumab appeared to be a highly effective treatment option for neovascular AMD with RAP. Further prospective studies are being carried out to evaluate the efficacy of ranibizumab in the treatment of RAP.

Reference

1. Bottoni F, Massacesi A, Cigada M, Viola F, Musicco I, Staurenghi G (2005) Treatment of retinal angiomatous proliferation in age-related macular degeneration. Arch Ophthalmol 123:1644–1650
2. Bottoni F, Romano M, Massacesi A, Bergamini F (2006) Remodeling of the vascular channels in retinal angiomatous proliferations treated with intravitreal triamcinolone acetonide and photodynamic therapy. Graefes Arch Clin Exp Ophthalmol 244:1528–1533
3. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S, ANCHOR Study Group (2006) Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 355:1432–1444
4. Donati MA, Carifi G, Virgili G, Menchini U (2006) Retinal angiomatous proliferation: association with clinical and angiographic features. Ophthalmologica 220:31–36
5. Fung AE, Lalwani GA, Rosenfeld PJ, Dubovy SR, Michels S, Feuer WJ, Puliafito CA, Davis JL, Flynn HW, Esquiabro M (2007) An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol 143:566–583
6. Freund KB, Klais CM, Eandi CM, Ober MD, Goldberg DE, Sorenson JA, Yannuzzi LA (2006) Sequenced combined intravitreal triamcinolone and indocyanine green angiography-guided photodynamic therapy for retinal angiomatous proliferation. Arch Ophthalmol 124:487–492
7. Joeres S, Heussen MA, Treziak T, Bopp S, Joussen AM (2007) Bevacizumab (Avastin) treatment in patients with retinal angiomatous proliferation. Graefes Arch Clin Exp Ophthalmol DOI 10.1007/s00417-007-0580-y
8. Meyerle CB, Freund KB, Iturralde D, Spaide RF, Sorenson JA, Slakter JS, Klancnik JM, Fisher YL, Cooney MJ, Yannuzzi LA (2007) Intravitreal bevacizumab (Avastin) for retinal angiomatous proliferation. Retina 27:451–457
9. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY, MARINA Study Group (2006) Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 355:1419–1431
10. Yannuzzi LA, Negrao S, Iida T, Carvalho C, Rodriguez-Coleman H, Slakter J, Fruend KB, Sorenson J, Orlock D, Borodoker N (2001) Retinal angiomatous proliferation in age-related macular degeneration. Retina 21:416–434