- regeneration in rat extraocular muscle. *Invest Ophthalmol Vis Sci* 1989;30:1643-51.
- 14 Phillips PH, Guyton DL, Hunter DG. Superior oblique overaction from local anesthesia for cataract surgery. *J AAPOS* 2001;5:329-32.
- 15 Khawam E, El-Dairi M, Al-Haddad C, et al. Inferior oblique overaction/contracture following

- retrobulbar anesthesia for cataract extraction with a positive Bielschowsky Head Tilt test to the contralateral filter. *Binocul Vis Strabismus Q* 2004;19:247-50.
- 16 Kim JH, Hwang JM. Imaging of the superior rectus in superior rectus overaction after retrobulbar anesthesia. *Ophthalmology* 2006;113:1681-4.

- 17 Scott B, Alexander DE, Miller, JM. Bupivacaine injection of eye muscles to treat strabismus. *Br J Ophthalmol* 2006;x:xxx.
- 18 Goldchmit M, Scott AB. Avaliacao da motilidade extrinseca ocular de pacientes facetectomizados sob anestesias retrobulbar. *Arq Bras Oftal* 1994;57:114-16.

Intravitreal Avastin

Intravitreal Avastin for choroidal neovascularisation in pathological myopia: the controversy continues

P J Rosenfeld

Intravitreal Avastin provides an opportunity to prevent visual acuity loss particularly in non-Western countries

In this issue, Yamamoto *et al*¹ and Sakaguchi *et al*² (see pages 157 and 161) are the first to report the use of intravitreal Avastin (bevacizumab; Genentech, Roche) for the treatment of subfoveal choroidal neovascularisation (CNV) secondary to pathological myopia. The use of intravitreal Avastin in this disease is a natural extension of the previous work with intravitreal Avastin in neovascular age related macular degeneration (AMD). Last year, Michels *et al*³ reported on systemic Avastin for the treatment of neovascular AMD in nine patients followed over 3 months, and this cohort was subsequently expanded to 18 patients followed over 6 months.⁴ During these 6 months, the authors observed a rapid and sustained improvement in visual acuity and anatomical outcomes. Following the report of these initial observations, a much smaller dose of Avastin was injected intravitreally in a patient with CNV from AMD and a patient with macular oedema from a central retinal vein occlusion.⁵⁻⁶ The anatomical improvements were rapid and appeared very similar to the results observed after the systemic infusion of Avastin. Since these two case reports were published, numerous publications have supported the *in vitro* and *in vivo* safety of intravitreal Avastin,⁷⁻¹⁵ and several retrospective reviews and one prospective study have reported impressive improvements in visual acuity, angiographic and optical coherence tomography (OCT) outcomes in patients with neovascular AMD and macular oedema.¹⁶⁻²⁰ Case reports have also shown dramatic improvements after administering intravitreal Avastin in eyes with proliferative diabetic retinopathy, neovascular glaucoma and cystoid macular oedema.²¹⁻²⁶

The same progression of events is now taking place in the use of Avastin for CNV secondary to pathological myopia. Last year, Nguyen *et al*²⁷ reported on the use of systemic Avastin for the treatment of subfoveal CNV secondary to pathological myopia in two patients. As with neovascular AMD, there was a reduction in angiographic leakage and OCT central retinal thickness after treatment in three eyes. These anatomical improvements were associated with visual acuity improvements in two of the three eyes. This report provided the first evidence that vascular endothelial growth factor-A played an important part in promoting CNV in pathological myopia. By inhibiting vascular endothelial growth factor-A with systemic Avastin, Nguyen *et al*²⁷ observed visual acuity and anatomical improvements that were not typical for normal disease progression. As the growth of CNV and the accompanying vision loss in neovascular pathological myopia are often not as predictable or severe as with CNV in AMD, the observed improvements in these patients were temporally related to the systemic infusion of Avastin and were unlikely to be the result of chance alone. Similar results have now been achieved after the intravitreal injection of Avastin.

Yamamoto *et al* report on a retrospective case series of 11 eyes from 9 patients injected with intravitreal Avastin. All patients were treated as part of their routine clinical care at the New England Eye Center (Boston, Massachusetts, USA). Of these 11 eyes, 5 eyes were previously treated with verteporfin photodynamic therapy (PDT). All eyes were followed by visual acuity, fluorescein angiography and OCT. As with systemic Avastin, intravitreal

Avastin resulted in both visual acuity and anatomical improvements that were temporally related to the treatment. With a mean follow-up of only 153 days, no conclusions are possible regarding the long-term benefits of intravitreal Avastin, but the short-term results appear promising. The average visual acuity improved 3.5-fold and the average OCT central foveal thickness measurement decreased by 103 µm. Overall, 10 of the 11 eyes showed improvement in visual acuity and 4 of the 5 eyes previously treated with PDT showed improvement as well. Only 3 of the 11 eyes received two injections each and the remaining 8 eyes received just one injection each, suggesting that frequent injections with Avastin may not be necessary.

Sakaguchi *et al* report on a prospective case series of 8 eyes from 8 patients injected with intravitreal Avastin. With a mean follow-up of only 4.4 months (range 3 to 7), the short term results once again appear very promising. Average visual acuity improved with 6 patients (75%) improving 2 or more lines. The mean OCT central foveal thickness measurement decreased by 43 microns. Only 3 of the 8 eyes received two injections each while the remaining 5 eyes received just one injection each once again suggesting that frequent injections with Avastin may not be necessary.

As no ocular or systemic adverse events were reported, there remains a theoretical risk that these eyes may be more susceptible to retinal tears and detachment after an intravitreal injection. It is impossible to draw any conclusions about safety from so few patients with such short follow-up, but these preliminary results do suggest that an eye with pathological myopia can tolerate an injection.

As with any retrospective review that examines a small number of patients with variable follow-up, there are many limitations that preclude generalisation of these results to all patients with neovascular pathological myopia. There is sure to be controversy as to whether it was ethical to use off-label intravitreal Avastin as primary treatment when PDT was approved and was available for the treatment of these patients. However, for those patients who were losing vision despite receiving PDT, the non-surgical options were limited. Treatment options included additional PDT, subtenons or intravitreal steroid, enrolment in the ongoing systemic Avastin study,²⁷ or the use of off-label intravitreal Avastin or Macugen (pegaptanib sodium;

Eyetech/OSI). For some, the potential risks associated with systemic Avastin might have made an intravitreal injection appear more attractive, and, among those choosing an injection, the low cost of intravitreal Avastin might have outweighed the known safety profile of Macugen.

This controversy will probably intensify now that Lucentis (ranibizumab; Genentech/Roche) is approved. In all likelihood, the efficacy of intravitreal Lucentis in pathological myopia will be comparable to, perhaps even better than, the results achieved with intravitreal Avastin. However, both drugs will be used off-label to treat neovascular pathological myopia. Lucentis has the advantage over Avastin in that it has been studied extensively in the eye and shown to be safe. However, the question remains whether Lucentis or Avastin should be used before PDT if PDT is the only treatment proved to be safe and effective, albeit only for 1 year. This has to be decided on between the doctor and the patient. Doctors and patients will need to discuss and weigh what is known about safety, efficacy and cost for any of these treatments. In those situations where patients have to pay for the drug, the cost of treatment will likely influence which drug is used. The option of using Avastin for \$17–\$50 a dose is clearly more attractive than PDT at \$1500 a treatment or Lucentis at \$2000 a dose. Eventually, for us to know which treatment is better, a head-to-head clinical trial is necessary.

In designing such a trial, we will need to avoid the problem encountered in the Verteporfin in Photodynamic (VIP) trial.^{28–29} The VIP trial, the only large, prospective, randomised treatment trial published for neovascular pathological myopia, investigated the role of PDT versus sham therapy over 2 years. The primary efficacy end point in this trial was to avoid a loss of eight letters from baseline, which differed from the primary end point in the neovascular AMD trials with PDT, where the loss of fewer than 15 letters was considered significant. This difference in primary end points was based on the presumed differences in disease progression and severity. Neovascular pathological myopia is a devastating disease affecting a population that is younger on average compared with AMD,^{30–31} and also a disease that is less predictable with variable progression. However, in an older population with myopia with CNV, the disease progression may be just as severe and predictable as in neovascular AMD.^{32–35} Most likely, because of this overall variability in disease progression, the VIP trial had too few patients to show a treatment benefit through 2 years. After 1 year, there was a significant benefit from treatment for the PDT group over the

sham group for the primary efficacy end point (72% v 44%; $p < 0.01$), but the significance of this benefit was lost in the second year (36% v 51%; $p = 0.11$) although the secondary efficacy end points clearly favoured PDT over sham. One possible explanation for the loss of significance was that the VIP trial was inadequately powered, with only 120 patients enrolled and 81 randomised to receive PDT compared with 39 in the sham group. In retrospect, based on the results after 2 years, the trial should have enrolled more patients at baseline to identify a statistically significant benefit after 2 years. However, even if statistical significance could have been achieved after 2 years, the treatment benefit was marginal and of questionable clinical relevance. In future trials to investigate intravitreal Avastin or Lucentis, this potential pitfall can be avoided by enrolling more patients. However, even if the next trial is adequately powered, the VIP trial warns us that positive results through 1 year may not necessarily translate into sustained benefits through 2 years, a concern that should make us wary of any short-term benefits observed with intravitreal Avastin in pathological myopia. On the other hand, the treatment benefits anticipated with intravitreal Avastin or Lucentis may far exceed the benefits observed with PDT.

Why should a prospective randomised clinical trial to investigate intravitreal Avastin for neovascular pathological myopia be performed? First and foremost, there is a huge unmet need to prevent blindness and vision impairment from pathological myopia. Whereas AMD is the major cause of irreversible vision loss among the elderly in Western countries, with 10–15% of patients developing CNV, pathological myopia is a major cause of irreversible vision loss in Asian countries and this vision loss affects a younger middle-aged population.^{33–40} As a result, the socioeconomic effect of vision loss from pathological myopia in Asian countries may be far greater than the effect of AMD in Western countries. In a recent paper by Xu *et al*,⁴⁰ pathological myopia was the second most common cause of visual impairment and blindness among 4439 participants in a population-based prevalence survey of adult Chinese people performed in the urban area and in the surrounding rural region of Beijing. As with AMD, only a small fraction of individuals with pathological myopia develop CNV, perhaps up to 10%,^{34–37–39} but the vision loss associated with neovascularisation can be the most severe. Although PDT may provide a marginal benefit for those who can afford the treatment, it is not available to most of the world's patients afflicted with neovascular pathological myopia, either because they do not have

access to PDT or because they are unable to afford the treatment. Other treatments for CNV include submacular surgery and macular translocation, but these are more expensive than PDT, require specialised facilities, and, much like Avastin, these surgical options have not yet been studied prospectively and shown to provide a benefit for at least a year or longer.³⁹

So, where do we go from here? Yamamoto *et al* and Sakaguchi *et al* have reported promising short-term results using off-label intravitreal Avastin for the treatment of CNV in pathological myopia. The availability of an inexpensive drug such as intravitreal Avastin provides an opportunity to prevent visual acuity loss, particularly in non-Western countries where the socioeconomic effect of neovascular pathological myopia is significant and the cost of Lucentis or PDT is prohibitive for many. A prospective clinical trial should be started, but who is going to cover the cost of such a trial? Genentech or Roche should not be expected to pay for an intravitreal Avastin clinical trial unless they plan to seek a labelled indication for Avastin in ophthalmology, which seems unlikely. Rather, the cost of such a trial is a societal responsibility of those agencies and governments that stand to benefit from preventing vision loss from neovascularisation in pathological myopia. It is time for clinicians to team up with governments, non-government organisations and foundations to design and support trials to investigate intravitreal Avastin for the treatment of CNV in pathological myopia.

Br J Ophthalmol 2006;**91**:128–130.
doi: 10.1136/bjo.2006.101337

Correspondence to: P J Rosenfeld, Bascom Palmer Eye Institute, University of Miami School of Medicine, 900 NW 17th Street, Miami, FL 33136, USA; prosenfeld@med.miami.edu

Competing interests: In the past 2 years, clinical research support has been received from Genentech, Eyetech/OSI Pharmaceuticals and Alcon Laboratories. Dr Rosenfeld has participated in scientific advisory boards on behalf of Genentech, Novartis Ophthalmics, Allergan, BioAxxone, PDL Biopharmaceuticals, Tanox, Jerini and Genaera. He also participates in the Genentech speakers' bureau.

REFERENCES

- 1 Yamamoto I, Rogers HA, Reichel E, *et al*. Intravitreal bevacizumab (Avastin) as treatment for subfoveal choroidal neovascularization secondary to pathologic myopia. *Br J Ophthalmol* 2007;**91**:157–60.
- 2 Sakaguchi H, Ikuno Y, Gomi F, *et al*. Intravitreal injection of bevacizumab for choroidal neovascularisation associated with pathological myopia. *Br J Ophthalmol* 2007;**91**:161–5.
- 3 Michels S, Rosenfeld PJ, Puliafito CA, *et al*. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology* 2005;**112**:1035–47.
- 4 Moshfeghi AA, Rosenfeld PJ, Puliafito CA, *et al*. Systemic bevacizumab (Avastin®) therapy for

- neovascular age-related macular degeneration: 24-week results of an uncontrolled, open-label clinical study. *Ophthalmology*. 2006; in press.
- 5 **Rosenfeld PJ**, Fung AE, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for macular edema from central retinal vein occlusion. *Ophthalmic Surg Lasers Imaging* 2005;**36**:336–9.
 - 6 **Rosenfeld PJ**, Moshfeghi AA, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmic Surg Lasers Imaging* 2005;**36**:331–5.
 - 7 **Shahar J**, Avery RL, Heilweil G, et al. Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin). *Retina* 2006;**26**:262–9.
 - 8 **Manzano RP**, Peyman GA, Khan P, et al. Testing intravitreal toxicity of bevacizumab (Avastin). *Retina* 2006;**26**:257–61.
 - 9 **Maturi RK**, Bleau LA, Wilson DL. Electrophysiologic findings after intravitreal bevacizumab (Avastin) treatment. *Retina* 2006;**26**:270–4.
 - 10 **Luthra S**, Narayanan R, Marques LE, et al. Evaluation of in vitro effects of bevacizumab (Avastin) on retinal pigment epithelial, neurosensory retinal, and microvascular endothelial cells. *Retina* 2006;**26**:512–18.
 - 11 **Fung AE**, Rosenfeld PJ, Reichel E. The international intravitreal bevacizumab safety survey: using the internet to assess drug safety worldwide. *Br J Ophthalmol*. 2006; in press.
 - 12 **Bakri SJ**, Snyder MR, Pulido JS, et al. Six-month stability of bevacizumab (Avastin) binding to vascular endothelial growth factor after withdrawal into a syringe and refrigeration or freezing. *Retina* 2006;**26**:519–22.
 - 13 **Bakri SJ**, Cameron JD, McCannel CA, et al. Absence of histologic retinal toxicity of intravitreal bevacizumab in a rabbit model. *Am J Ophthalmol* 2006;**142**:162–4.
 - 14 **Luke M**, Wargha M, Ziemssen F, et al. Effects of bevacizumab on retinal function in isolated vertebrate retina. *Br J Ophthalmol* 2006;**90**:1178–82.
 - 15 **Spitzer MS**, Wallenfels-Thilo B, Sierra A, et al. Antiproliferative and cytotoxic properties of bevacizumab (Avastin) on different ocular cells. *Br J Ophthalmol*. 2006; in press.
 - 16 **Avery RL**, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology*. 2006;**113**:363–72, e5.
 - 17 **Spaide RF**, Laud K, Fine HF, et al. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006;**26**:383–90.
 - 18 **Rich RM**, Rosenfeld PJ, Puliafito CA, et al. Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Retina* 2006;**26**:495–511.
 - 19 **Iturralde D**, Spaide RF, Meyerle CB, et al. Intravitreal bevacizumab (Avastin) treatment of macular edema in central retinal vein occlusion: a short-term study. *Retina* 2006;**26**:279–84.
 - 20 **Bashshur ZF**, Bazarbachi A, Schakal A, et al. Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration. *Am J Ophthalmol* 2006;**142**:1–9.
 - 21 **Avery RL**. Regression of retinal and iris neovascularization after intravitreal bevacizumab (Avastin) treatment. *Retina* 2006;**26**:352–4.
 - 22 **Bakri SJ**, Donaldson MJ, Link TP. Rapid regression of disc neovascularization in a patient with proliferative diabetic retinopathy following adjunctive intravitreal bevacizumab. *Eye*. 2006; in press.
 - 23 **Davidoff FH**, Mouser JG, Derick RJ. Rapid improvement of rubeosis iridis from a single bevacizumab (avastin) injection. *Retina* 2006;**26**:354–6.
 - 24 **Kahook MY**, Schuman JS, Noecker RJ. Intravitreal bevacizumab in a patient with neovascular glaucoma. *Ophthalmic Surg Lasers Imaging* 2006;**37**:144–6.
 - 25 **Spaide RF**, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. *Retina* 2006;**26**:275–8.
 - 26 **Mason JO III**, Albert MA Jr, Vail R. Intravitreal bevacizumab (Avastin) for refractory pseudophakic cystoid macular edema. *Retina* 2006;**26**:356–7.
 - 27 **Nguyen QD**, Shah S, Tatlipinar S, et al. Bevacizumab suppresses choroidal neovascularisation caused by pathological myopia. *Br J Ophthalmol* 2005;**89**:1368–70.
 - 28 **VIP Study Group**. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial—VIP report no. 1. *Ophthalmology* 2001;**108**:841–52.
 - 29 **VIP Study Group**. Verteporfin therapy of subfoveal choroidal neovascularization in pathologic myopia: 2-year results of a randomized clinical trial—VIP report no. 3. *Ophthalmology* 2003;**110**:667–73.
 - 30 **Cohen SY**, Laroché A, Leguen Y, et al. Etiology of choroidal neovascularization in young patients. *Ophthalmology* 1996;**103**:1241–4.
 - 31 **Spaide RF**. Choroidal neovascularization in younger patients. *Curr Opin Ophthalmol* 1999;**10**:177–81.
 - 32 **Tabandeh H**, Flynn HW Jr, Scott IU, et al. Visual acuity outcomes of patients 50 years of age and older with high myopia and untreated choroidal neovascularization. *Ophthalmology* 1999;**106**:2063–7.
 - 33 **Yoshida T**, Ohno-Matsui K, Ohtake Y, et al. Long-term visual prognosis of choroidal neovascularization in high myopia: a comparison between age groups. *Ophthalmology* 2002;**109**:712–19.
 - 34 **Yoshida T**, Ohno-Matsui K, Yasuzumi K, et al. Myopic choroidal neovascularization: a 10-year follow-up. *Ophthalmology* 2003;**110**:1297–305.
 - 35 **Kojima A**, Ohno-Matsui K, Teramukai S, et al. Estimation of visual outcome without treatment in patients with subfoveal choroidal neovascularization in pathologic myopia. *Graefes Arch Clin Exp Ophthalmol*, 2006 Apr 21; [Epub ahead of print].
 - 36 **Liu JH**, Cheng CY, Chen SJ, et al. Visual impairment in a Taiwanese population: prevalence, causes, and socioeconomic factors. *Ophthalmic Epidemiol* 2001;**8**:339–50.
 - 37 **Ohno-Matsui K**, Yoshida T, Futagami S, et al. Patchy atrophy and lacquer cracks predispose to the development of choroidal neovascularisation in pathological myopia. *Br J Ophthalmol* 2003;**87**:570–3.
 - 38 **Hsu WM**, Cheng CY, Liu JH, et al. Prevalence and causes of visual impairment in an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Ophthalmology* 2004;**111**:62–9.
 - 39 **Chan WM**, Ohji M, Lai TY, et al. Choroidal neovascularisation in pathological myopia: an update in management. *Br J Ophthalmol* 2005;**89**:1522–8.
 - 40 **Xu L**, Wang Y, Li Y, et al. Causes of blindness and visual impairment in urban and rural areas in Beijing: the Beijing Eye Study. *Ophthalmology* 2006;**113**:e1–3.

Immunohistochemical analysis and neovascular AMD

Towards a rational approach to combination therapy for neovascular age-related macular degeneration

Jorge G Arroyo

Multifactorial Immunohistochemical Analysis of Choroidal Neovascularisation

Neovascularisation is controlled by the temporal and spatial distribution of agonising and antagonising membrane-bound and diffusible substances.¹ In 1948, Michaelson² hypothesised that a diffusible, hypoxia-induced, angiogenic “factor X” was responsible for iris and retinal neovascularisation associated with ischaemic retinopathies.

Decades later, in 1983, a candidate glycoprotein was partially characterised by Dvorak *et al*³ and initially termed vascular permeability factor. Further work by Ferrara and Henzel⁴ expanded our understanding of this endothelial cell-specific glycoprotein, leading to its current name, vascular endothelial growth factor (VEGF). Since then,

researchers have carried out studies on both animals and humans that strongly suggest that the diffusible, hypoxia-induced, endothelial cell-specific factor VEGF^{5–7} most probably represents Michelson’s retinal tissue “factor X”.

The fields of oncology and ophthalmology have profited from the discovery of VEGF and its critical role in physiological and pathological neovascularisation. The development of various antagonists, such as antibodies, antibody fragments, aptamers, traps, small interfering RNA fragments, has resulted in a leap forward in the treatment of neovascularisation associated with age-related macular degeneration (AMD),^{8–9} an oxidative/ischaemic/inflammatory retinopathy, and promises to make important inroads in the treatment of neovascularisation associated with ischaemic retinopathies, such as diabetic retinopathy, retinal vein occlusions and retinopathy of prematurity.

As with most biological systems, physiological neovascularisation is controlled by a dynamic balance between positive and