Intravitreal Avastin

Intravitreal Avastin for choroidal neovascularisation in pathological myopia: the controversy continues
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Intravitreal Avastin provides an opportunity to prevent visual acuity loss particularly in non-Western countries

I n this issue, Yamamoto et al1 and Sakaguchi et al2 (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 al3 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 al27 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 al28 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. 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 8 eyes received just one injection each, 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,29 or the use of off-label intravitreal Avastin or Macugen (pegaptanib sodium: 17 Scott B, Alexander DE, Miller, JM. Bupivacaine injection of eye muscles to treat strabismus. Br J Ophthalmol 2006;
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.26-29 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 or 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.36-40 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.,41 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 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 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 affected 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.42

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.


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

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Multifactorial Immunohistochemical Analysis of Choroidal Neovascularisation

Neovascularisation is controlled by the temporal and spatial distribution of angiogenic and antiangiogenic factors. In 1948, Michelson 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. and initially termed vascular permeability factor. Further work by Ferrara and Henzel 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-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). An oxidative/ischaemic inflammatory retinochoroidopathy, 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