Anti-vascular endothelial growth factor therapies in ophthalmology: current use, controversies and the future

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Use of anti-vascular endothelial growth factor (VEGF) therapies was introduced for the treatment of ocular disorders in 2005. In the UK, the current licensed and NICE approved indications are for the treatment of neovascular age-related macular degeneration (nAMD), diabetic macular oedema (DMO), macular oedema secondary to a retinal vein occlusion (RVO) and choroidal neovascularization in pathological myopia. These diagnoses alone account for two-thirds of the main causes of legally registrable visual impairment and blindness. Ranibizumab (Lucentis®; Genentech/Novartis), a drug specifically designed for intraocular use, is the primary licensed medication. Controversially however, clinicians have been using an unlicensed cheaper drug, bevacizumab (Avastin®; Genentech/Roche), originally designed for systemic administration, with a similar mode of action and shown to have a similar efficacy. However, there are fears of greater side effects with bevacizumab though studies have not been sufficiently powered to show statistical difference. In the current global economic climate, anti-VEGF treatment places huge financial and logistical pressure on already strained health care systems. Bevacizumab is considerably more cost effective than ranibizumab, and thus using bevacizumab would widen access to treatment particularly in developing countries. This licensing issue also places clinicians in a difficult medico-legal position especially in Europe, where doctors are duty bound to use a licensed drug for a particular indication if this is available. As the indications of anti-VEGF therapies expand and the cost of health care provision becomes more expensive, the controversies surrounding their use will inevitably become more important.

Introduction

Vascular endothelial growth factor (VEGF), discovered over 20 years ago, is a key regulator in the proliferation and migration of vascular endothelial cells [1], as well as in promotion of vasodilatation and vascular permeability. It plays a critical role in the process of vasculogenesis and angiogenesis [2], which in turn is involved in many physiological processes, such as wound healing, reproduction and organ development. Vascular endothelial growth factor also plays a major role in pathological neovascularization, particularly in the development of solid tumours [3] and a number of sight-threatening diseases [4].

VEGF is a heparin-binding mitogen, which exists as a dimeric glycoprotein, approximately 40 kDa in size. The human *VEGF* gene is located on chromosome 6p21.3 and consists of eight exons interspersed with seven introns [5]. There are seven main members of the VEGF family (A–F, PGF) but alternative exon splicing increases the number of VEGF variants. In the human eye, VEGF-A is believed to play the greatest role and primarily exists as VEGF-A 121, VEGF-A 165 (most common), VEGF-A 189 and VEGF-A 206 isoforms [6], but four other isoforms also exist.

There are three main VEGF receptors, known as VEGFR-1, VEGFR-2 and VEGFR-3, which exist as both membrane-bound and soluble forms; VEGF-A appears to bind only with receptors 1 and 2.

Vascular endothelial growth factor in the eye

VEGF-A has been shown to be produced by different cells within the retina, such as Müller cells, retinal pigment epithelial cells [7] and vascular endothelium [8], where

hypoxia is a major stimulator for its production. *In situ* hybridization studies have demonstrated upregulation of *VEGF-A* mRNA expression in retinal cells in patients suffering from proliferative retinopathies secondary to diabetes and central retinal vein occlusions [9]. VEGF-A 165, the primary isoform found in the eye, also appears to be the isoform responsible for pathological ocular neovascularization [10–12]; however, VEGF-A 121 also seems to be essential for normal retinal vascular function [11]. Emerging data suggest that the other isoforms have key roles in tissue homeostasis, such as maintenance of the choriocapillaris [13] and cell volume regulation of glial tissue in the retina [14], as well as other diverse roles in neuronal regulation [15] and neuronal development in the brain [16].

Common conditions in which VEGF plays a significant role include neovascular age-related macular degeneration (nAMD) [17, 18], diabetic retinopathy [19] and retinal vascular occlusive disease, as well as less common conditions, such as retinopathy of prematurity [20], sickle cell disease [21], neovascular glaucoma [22] and certain retinal dystrophies [23].

Anti-VEGF therapies

It was first reported in 1993 that anti-VEGF monoclonal antibodies inhibited the growth of many tumour cell lines in nude mice experiments [24]. Subsequently, an anti-VEGF monocolonal antibody (bevacizumab) was discovered to decrease tumour perfusion, vascular volume and microvascular density in patients with colorectal cancer and thus demonstrates that VEGF blockade results in a direct anti-vascular effect on human tumours [25].

Whilst the first commercially available anti-VEGF therapy (Macugen®; Pfizer) was highly selective, targeting VEGF-A 165 alone, all the subsequent therapies that have been more efficacious have a pan-anti-VEGF activity across all isoforms. The risks and adverse effects of such nontargeted therapy however are not yet fully understood [26]. These injections are being used even in neonates for retinopathy of prematurity; this is undoubtedly a high-risk group, but firm reports of adverse outcomes in neuronal development have not yet been reported [27]. This risk must, of course, be balanced against the alternative outcome of blinding disease in a neonate.

The drugs

The first drug obtaining US Food and Drug Administration (FDA) approval, in December 2004, was pegaptanib (Macugen®; Pfizer) for the use in nAMD. It is a small RNA aptamer, which preferentially binds to the heparin-binding domain of the VEGF-A 165 isoform, which is primarily responsible for pathological retinal neovas-

cularization and vascular permeability [28]. This structural specificity is thought to limit interaction with other isoforms and thus prevent major systemic vascular events. Studies, however, show a modest efficacy, which may be explained by the relative short half-life of VEGF-A 165 compared with other VEGF isoforms in the eye [29, 30].

In 2004, bevacizumab (Avastin®; Genentech) was approved by the US FDA for the use in colorectal cancer. It is a full-length humanized monoclonal antibody (149 kDa) with two VEGF-A-binding sites that binds all isoforms of VEGF-A. Rosenfeld at the Bascom Palmer Eye Institute, Miami, noticed that systemically administered bevacizumab resulted in improvement in visual acuity, ocular coherence tomography and angiographic parameters, in addition to promising evidence of safety [31]. This led to the same group evaluating the short-term safety and efficacy of intravitreal administration of bevacizumab, with impressive results [32]. Until recently, initial and continued use of bevacizumab was based mainly on observational data and clinical experience, with a relative paucity of strong level 1 evidence. However, the ABC trial, a double-masked, randomized controlled trial (RCT) comparing bevacizumab with standard treatment of nAMD showed significant improvement of visual acuity in the bevacizumab group [33]. Subsequent robust trails, such as the CATT, IVAN and MANTA head-to-head comparisons of ranibizumab and bevacizumab have vindicated their usage, essentially confirming that non-inferiority was not demonstrated [34–38].

In 2006, the US FDA approved the use of ranubizumab (Lucentis®; Genentech/Novartis), which was developed specifically for intraocular use. It is a fragment antigen-binding region of the humanized antibody (Fab) with a molecular mass of 48 kDa, produced by a bacterial vector recombinant process with 100 times binding affinity to all isoforms of VEGF. Theoretically, without the fragment crystallizable region (Fc), the smaller molecule should have greater retinal penetration but a shorter half-life.

A far greater number of high-quality studies are available for ranibizumab, especially in the treatment of nAMD. Two seminal large phase III RCTs, called the ANCHOR [39] and MARINA [40] studies, provide strong evidence of the superior efficacy of ranibizumab over both standard treatments of that time (i.e. photodynamic therapy) and sham, respectively. The dramatic visual and anatomical benefits seen with this agent led to a dramatic decline in the use of pegaptanib.

In November 2011, the FDA approved the latest drug, aflibercept (EYLEA®; Bayer), for the treatment of nAMD. It is a soluble fusion protein consisting of extracellular VEGF-binding domains derived from VEGFR-1 and VEGFR-2, fused to the Fc segment of human IgG. Aflibercept shows high affinity for VEGF-A, VEGF-B and placental growth factors 1 and 2 [41]. With a reported VEGF-binding affinity 140 times that of ranibizumab [42], binding can last 10–12 weeks, nearly twice as long as ranibizumab and

Table 1

Current ocular disease authorized to be treated with anti-vascular endothelial growth factor (anti-VEGF) drugs by the National Institute for Clinical Excellence (NICE) and potential ocular diseases which are currently being studied

Disease	NICE-authorized anti-VEGF
Choroidal neovascularization secondary to age-related macular degeneration*	Ranibizumab, aflibercept
Macular oedema following central retinal vein occlusion*	Ranibizumab, aflibercept
Macular oedema following branch retinal vein occlusion*	Ranibizumab
Diabetic macula oedema*	Ranibizumab
Choroidal neovascularization secondary to pathological myopia*	Ranibizumab
Potential disease targets being studied	
Polypoidal choroidopathy	
Retinopathy of prematurity	
Neovascular glaucoma	
Sickle cell retinopathy	
Proliferative diabetic retinopathy	
Juxtafoveal telangectasia	
Corneal neovascularization	

*UK licensed indications for ranibizumab and aflibercept. See http://www.ema.europa.eu/ for full European guidance.

bevacizumab [43]. Recent double-masked RCTs, the VIEW 1 and VIEW 2, studies show favourable results in the treatment of nAMD [44]. Importantly, they show that bimonthly aflibercept was not worse than monthly ranibizumab at preventing loss of vision, with similar visual outcomes and safety profiles. A further breakthrough seen is enhanced efficacy in cases deemed suboptimally responsive to ranibizumab and better anatomical outcomes with retinal pigment epithelial detachments, abnormalities that were typically very poorly responsive to the other anti-VEGF agents [45, 46]. Despite a similar price of the drug to ranibizumab, the bimonthly treatment regimen would result in significant cost savings over current ranibizumab treatment. In addition, it increases clinic capacity to deliver additional injection services, and is much more preferable from the patient's perspective to attend every 2 months rather than 4 weekly.

The aforementioned anti-VEGF drugs have primarily been studied in the context of nAMD; however, their use has recently started to include other ocular conditons where neovascularization and vessel leakage play important roles (Table 1). This year alone, following detailed appraisal of these technologies, NICE (the National Institute of Clinical Excellence, UK) has authorized the use of ranibizumab for diabetic macular oedema, macular oedema following retinal vein occlusion and choroidal neovascularization in pathological myopia, whilst aflibercept has been authorized for nAMD and central retinal vein occlusions. These conditions alone account for two-thirds of all blindness registrations in the UK [47].

Controversies and issues

Currently, opinion is divided regarding which anti-VEGF treatment should be used to treat the burgeoning ophthalmic patient population. Bevacizumab and ranibizumab are still the two most commonly used anti-VEGF drugs, but aflibercept has shown rapid uptake and is expected to take half the market share within the next 2 years [48].

However, much controversy exists, because there is a significant cost difference between the drugs in addition to the fact that bevacizumab is not licensed for intraocular administration.

Cost

The primary driving factor for clinicians, particularly in developing nations, to continue to use bevacizumab despite the introduction of ocular specific ranibizumab is the extreme cost differential. Bevacizumab is not produced as an intraocular preparation but is instead processed from the systemically administered preparation originally intended for cancer patients.

In the USA, a 100 mg 4 ml vial of bevacizumab cost merely $550. With much smaller aliquots of the drug being needed for intraocular use, each intraocular dose therefore costs less than $50. Ranibizumab, in contrast, has a whole salecost of $1950 for a single 0.5 mg dose [49]. Recent cost utility analysis evaluated incremental cost effectiveness from a US payer perspective [50]. The cost effectiveness ratios were $1405 per quality-adjusted life year (QALY) for bevacizumab as opposed to $12 177 per QALY for ranibizumab. Markov modelling of cost effectiveness from a UK perspective revealed that in order to achieve the NICE threshold of £30 000 per QALY and thus be considered cost effective in relation to bevacizumab, ranibizumab would have to be at least twice as efficacious [51], which it is not.

From a UK National Health Service (NHS) perspective, a large UK-based multicentre trial compared the cost between bevacizumab and ranibizumab [36]. Annual patient costs were calculated using NICE established guidelines and included monitoring, adverse events and drugs costs [52]. The study also compared dosing regimens either as continuous monthly or discontinuous treatments as needed. At the time, the UK drug cost of ranibizumab was £742.17 per dose compared with £49 per dose for bevacizumab. The most expensive course of treatment involved monthly ranibizumab treatment, with a total cost of £9656 per patient per year, the majority of which comprised drug costs (£8494). Discontinuous (essentially *pro re nata*) treatment with ranibizumab was next most expensive, with an annual cost of £6398 per patient per year. Bevacizumab, unsurprisingly, had a lower total cost of £1654 and £1509 per patient per year for continuous and discontinuous treatment regimens, respectively. Interestingly, the costs for monitoring and

managing expected adverse events were not significantly different between the two drugs. When extrapolated to include all patients in the NHS treated on a discontinuous basis, a potential annual saving of £84.5 million could be made.

Even the optimal dosing regimen has not been investigated adequately; the posology states 4 weekly injections, but the majority of clinicians use *pro re nata* injections, guided by signs of disease activity on optical coherence tomography scanning of the retina.

Recently, in September 2011, a cluster of Primary Care Trusts (SHIP: Southampton, Hampshire, Isle of Wight and Portsmouth) made a bold move to allow use of the unlicensed drug Avastin, but when faced with the threat of a judicial review, after Novartis sought a challenge on the legality of this option, this commissioning policy was revoked [53].

Safety

Advocates of ranibizumab highlight fears that using bevacizumab may potentially expose patients to additional adverse ocular and systemic side-effects. As bevacizumab is a complete antibody, there is a theoretical risk that the Fc segment could cause greater intraocular inflammation. The systemic half-life is also more than double that of ranibizumab [54] when administered intravitreally, which may potentially lead to increased systemic side-effects. It is already well reported that bevacizumab, when used systemically in oncology treatments, results in increased rates of thromboembolic events, cardiac ischaemia [55], haemorrhage [56] and death [57]. It must be noted, however, that these patients were terminally ill with metastatic disease, and were receiving an intravenous dose 400 times greater than the ocular dose, in a single bolus, whilst the ocularly administered drug seeps more slowly into the circulation.

Currently, different manufacturing and preparation processes exist between the drugs, as bevacizumab is produced as an intravenous preparation, which then needs to be processed for intraocular use, whereas ranibizumab requires no further processing. The lack of preservatives and different manufacturing standards between intravenous and intraocular preparations is feared to result in increased rates of sterile or infective endophthalmitis, although no studies have shown this to be the case.

There are great difficulties when trying to draw a conclusion regarding relative safety, due to the rarity of both ocular and systemic side-effects, the lack of postmarketing surveillance and the fact that studies have involved insufficient numbers of patients to be powered to draw conclusions. There are also doubts regarding the significance of suppression of serum VEGF levels, which has been reported with bevacizumab [58, 59]. The significant adverse events that have been reported in patients given bevacizumab are not those expected with systemic VEGF suppression. Recent studies, however, comparing the

drugs for the treatment of nAMD have revealed only minor differences in safety profiles over 1–2 years [35, 36].

Licensing

A unique situation exists with ranibizumab, which is a licensed treatment for intraocular use, and bevacizumab, which is not licensed for ocular use, despite substantial evidence for their similar efficacy and safety profiles. Usually, the licensing process involves the pharmaceutical company applying to the relevent national and international regulatory authoities in order to seek a licence or regulatory approval for a drug to be used. In the UK, the Medicines and Healthcare products Regulatory Authority (MHRA) along with the European Medicines Agency (EMA) ensure that the medicinal product fulfils the legislative requirements on safety, quality and efficacy dictated by European Community (EC) law, which is currently defined by the directive 2001/83/EC.

In this circumstance, one company (Genentech) has ownership of both these class-leading but competing drugs. By not licencing bevacizumab, the anti-VEGF market is less competitive, with the associated financial benefit evident for the industry. The criticisms of the pharmaceutical industry have been accusations of profiteering and protection of a lucrative product rather than claims about patient safety. However, the counter-argument is that going through licensing would be an extremely expensive and time-consuming process to establish the relevant trial data, with no financial benefit to the company.

Legalities

The continued and popular 'off-label' use of bevacizumab has placed this recently developed type of treatment for nAMD in a unique dilemma. Despite the availability of the ocular specific ranibizumab, analysis of Medicare fee-for-service revealed that bevacizumab was the most popular choice in the USA for nAMD treatment, with nearly 60% of anti-VEGF injections in 2008 [60].

General Medical Council (GMC) guidelines recommend that 'when prescribing a drug outside the terms of its licence you must be satisfied that it would better serve the patient's needs than an appropriately licensed alternative'. The GMC has further stated that 'serious or persistent failure to follow this guidance will put your registration at risk'. The professional body representing ophthalmologists in the UK, the Royal College of Ophthalmologists, published guidance in December 2011 supporting the continued use of Lucentis rather than Avastin. Although studies have shown 'non-inferiority' of bevacizumab compared with ranibizumab, none has demonstrated better outcomes. Bevacizumab use therefore contravenes national guidance and places the clinician in a difficult medicolegal position.

As a result, in the UK, there is no advantage for an individual clinician to use unlicensed bevacizumab, con-

sidering that treatment is publically funded and with the threat of litigation from the patient or manufacturer.

The future

Although the majority of anti-VEGF trials have involved nAMD and diabetic eye disease, the number of indications will continue to increase as more ocular conditions are showing promising responses.

The current trend for these treatments is to increase the duration of action and thus reduce number of treatments and hospital visits. The recent introduction of aflibercept can potentially reduce the frequency of patient visits by at least half. This will have obvious financial benefits, with reduced drug and monitoring costs. Another promising treatment that requires less frequent dosage is fluocinolone acetonide intravitreal implant (Iluvien®; Alimera Sciences), recently approved in the use of chronic diabetic macular oedema. This corticosteroid implant can potentially last up to 3 years, via a unique slow-release delivery system [61].

It is important to note that none of the aforementioned treatments can be considered a cure and they are really a means of control only. The long-term effects of repeated anti-VEGF injections are unknown, although there are observations of geographic atrophy, a severe variant of dry age-related macular degeneration, which is unresponsive to further anti-VEGF treatments and eventually leads to permanent visual loss.

If anti-VEGF treatments in their current form are insufficient to improve vision significantly or to provide longer term visual stability, perhaps the future lies in combination with other anti-inflammatory and anti-fibrotic therapies. Such combination approaches are common in other areas of medicine, especially oncology, representing a necessary multitarget approach to these complex diseases. Approaches showing promise include the use of novel agents, such as Fovista™ (an anti-platelet-derived growth factor agent) whose unpublished phase 2b data are promising 62% additional visual benefit at the primary endpoint. A nanoparticle approach is also being investigated, with exciting results in murine and primate models of macular degeneration [62].

From a pharmaceutical industry perspective, bevacizumab is soon to come off patent in 2015, which may allow other firms to apply for licensing. This could potentially create more competition in the market, thus possibly driving down prices, making them more affordable to healthcare providers and patients. In contrast, this may paradoxically reduce any potential future investment and research into this field, because any new agents will need to be either more cost effective than bevacizumab or significantly more efficacious in order to justify widespread adoption. The already low cost of bevacizumab may, in this respect, be difficult for new agents to beat, hence unattractive for pharmaceutical firms to invest in.

Conclusions

Anti-VEGF treatments have had and will continue to have a tremendous impact on the burden of disorders which together make up a large proportion of irreversible vision loss. With an ageing population and incidence of diseases such as macular degeneration and diabetes expected to double over the next decade, these drugs will undoubtedly have increasing importance.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; MM has received personal fees from Alcon, Alimera Sciences, Bausch and Lomb, Allergan, Bayer and Novartis in the previous 3 years; TQK has no financial relationships with any organizations that may have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

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