Anti-VEGF in the treatment of AMD

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Background

Since the begining of the last century much attention has been focused on tumour vascularization.

Warren Lewis(1), in 1922, and Gordon Ide, in 1939(2), had already considered the hypothesis of synthesis of a vascular growth factor by tumour cells.

Synthesis of a vascular growth factor in the retina was proposed for the first time in 1948(3), in diabetic eyes by Isaac Michelson.

In the beginning of 1970, Folkman and his research group demonstrated that tumour growth is directly related to tumour vascularization, which, in turn, depends on the expression of certain growth factors(4).

Vascular endothelial growth – VEGF

Harold Dvorak's group(5), who identified the Tumour Vascular Permeability Factor (VPF), which causes vascular hyperpermeability, in tumour cells from guinea pigs.

In 1989, 3 groups, including Ferrara et al, published articles highlighting a molecule with pro-mitotic properties in endothelial cells.

Ferrara et al. identified this protein in bovines, having named it Vascular Endothelial Growth Factor (VEGF), the term by which it has been known since then(6,7,8).

VEGF-A, a molecule involved in eye diseases such as Age-related Macular Degeneration (AMD) and diabetic retinopathy, is part of a family of genes that also includes VEGF-B, C and D, and the viral homologue VEGF-E, in addition to the Placental Growth Factor – PlGF.

VEGF-A, which has been extensively studied, is a dimeric 36-46 kd glycosylated protein with an N-terminal signal sequence and a heparin-binding domain(9,10).

Four different VEGF-A isoforms have been identified in humans with varying numbers of amino acids: VEGF121, VEGF 165, VEGF 189 and VEGF 206.

They arise from alternative splicing of mRNA.

The longer forms are matrix-bound and the shorter forms are freely diffusible.

VEGF 165 is the dominant isoform in ocular neovascularization processes(11).

VEGF receptors

Three VEGF receptors have been identified: VEGFR-1 (fms-like tyrosine kinase-1 or Flt-1), VEGFR-2 (kinase insert domain-containing receptor or KDR) and VEGFR-3 (fms-like tyrosine kinase-4 or Flt-4), which is a receptor for VEGF-C and VEGF-D.

VEGF-A binds both to the R1 and R2 receptors.

VEGFR-2 is considered the main VEGF mediator in endothelial cells.

Its activation induces NO (nitric oxide) production, cell membrane and cytoskeleton reorganisation and proliferation and migration of endothelial cells.

It is also involved in the activation of the phosphatidylinositol 3-kinase (PI3)Akt pathway, which is a crucial signal transduction pathway in the process leading to endothelial cell survival induced by VEGF-A[(12)].

Physiology of VEGF

VEGF-A is an important permeability inducer and is about 50,000 times more potent than histamine.

It is also a potent mitogen in endothelial cells and may have an important role in maturing of new blood vessels through pericytes[(13)].

VEGF-A is involved in physiological angiogenesis in adults, for example, in the female reproduction cycle[(14)].

In addition, VEGF-A mRNA is expressed in various healthy human adult tissues that do not show angiogenesis, such as the epithelium of the choroid plexus in the brain, the glomerular epithelium in the kidney, the gastrointestinal mucosa and hair follicles[(15)].

It has been suggested that VEGF-A maintains the integrity of endothelial cells via anti-apoptotic signalling[(15)].

VEGF-A has been recognised as an important neuroprotectant in the central nervous system.

VEGF-A exposure resulted in a dose-dependent reduction in retinal neuronal apoptosis[(16)].

Although mechanistic studies have suggested that VEGF-induced volumetric blood flow to the retina may be partially responsible for neuroprotection, ex vivo retinal cultures have revealed a direct neuroprotective effect for VEGF-A.

VEGF receptor-2 expression has been detected in several neuronal cell layers of the retina, and functional analyses have shown that VEGFR-2 is involved in retinal neuroprotection[(16)].

It has been shown that VEGF-A is secreted by Retinal Pigment Epithelial (RPE) cells, on their basal side, i.e. the side adjacent to the choriocapillaris, and the 3 VEGFRs are expressed in choriocapillaris endothelial cells, on the side facing retinal pigment epithelial cells.

It has long been known that loss of RPE cells in the human eye causes atrophy of the choriocapillaris.

These findings are consistent with a role of VEGF-A secreted by RPE cells as a permeability/survival factor for quiescent choriocapillaris endothelium[(17)].

Since VEGF is highly regulated by hypoxia, a feedback mechanism must exist in these epithelia to promote physiological formation of new blood vessels when tissue oxygenation is low.

Unbalances in this mechanism may cause serious diseases, such as Exudative Age-related Macular Degeneration (AMD)[(15)].

VEGF and pathology

The predominant role of VEGF-A in the development of pathological angiogenesis, such as that occurring in tumours and ischaemic and inflammatory processes was widely demonstrated in the last decade[(18)].

In hypoxic states, VEGF is secreted by RPE cells[(19)].

This factor induces endothelial cell proliferation and increases vascular permeability.

It has been shown in several models that VEGF-A is required and sufficient for development of new blood vessels in the retina and the iris.

s already mentioned, VEGF-A has been identified as a primordial factor in the neovascular response induced by retinal ischaemia.

Therefore, VEGF-A levels are increased in the vitreous and retina of patients with neovascularization secondary to proliferative diabetic retinopathy, venous occlusion or retinopathy of prematurity[20-23]. In clinical practice, observed blood VEGF levels are increased in AMD patients[24].

Many studies have revealed VEGF overexpression in neovascular membranes during autopsy procedures or after surgical extraction[25,26].

Since 1996, immunohistochemistry studies of frozen sections of neovascular membranes have shown significant VEGF levels in highly vascularized regions, although lower immunoreactivity has been observed in fibrotic membrane regions[28,29].

Drusens and basal linear deposits have also been associated with high VEGF levels[30].

Therefore, vascular endothelial growth factor A (VEGF-A) regulates angiogenesis and vascular permeability in the eye, both in physiological and pathological processes.

This growth factor selectively influences endothelial cell growth, being particularly responsible for increased vascular permeability.

It also plays a role in the survival of many cells. Inhibition of neovascularization – the cause of exudative or neovascular AMD – was the basis of some disease-modifying therapies, since anti-VEGFs may delay or even halt disease progression.

The vascular endothelial growth factor is a secreted protein that induces angiogenesis and increases vascular permeability and inflammation, which appear to contribute to neovascular AMD progression. Naturally, VEGF is the target of investigational drugs for the treatment of AMD[31,32].

It is possible to inhibit every step of the angiogenesis cascade induced by VEGF: VEGF synthesis may be inhibited by inhibiting the synthesis of the corresponding mRNA or by inhibiting transcription[33].

The effect of VEGF may also be directly inhibited , by inhibiting protein action.

This is the mechanism used in anti-VEGF therapies[34,35]. Angiogenesis may also be inhibited after VEGF binding, as occurs with anecortave acetate and squalamine lactate[36-38].

Treatment of AMD with anti-VEGFs is thus considered to be a turning point since its emergence has allowed a more direct approach to choroidal neovascularization and its selective inhibition.

Therefore, anti-VEGF treatments offer new hope to thousands of neovascular AMD patients, a disease that used to be understood as an untreatable condition associated with ageing before the emergence of anti-VEGF drugs.

These drugs are particularly effective in the early stages of the disease, when newly formed blood vessels are less mature: inhibition of their growth allows photoreceptors to remain viable, as well as reducing the risk of central fibrosis and delaying progressive loss of vision.

Three drugs in this class are currently used in the treatment of AMD: pegaptanib (Macugen®), ranibizumab (Lucentis®) and bevacizumab (Avastin®), of which only the first two have been approved for this therapeutic indication.

Ranibizumab (Lucentis®)

Ranibizumab is a Fab fragment of a recombinant humanized monoclonal antibody with high affinity for VEGF-A (the ranibizumab binding site has an affinity for binding VEGF-A 140-fold higher than that displayed by the bevacizumab binding site) specifically studied for the treatment of AMD[39,40,41].

Ranibizumab has a solid clinical development program for this therapeutic indication, involving over 7,000 patients.

Ranibizumab binds to an amino acid chain common to all VEGF-A isoforms, thus rendering them inactive, reducing retinal and choroidal angiogenesis and halting the increase in capillary permeability.

It has been shown in animal models that ranibizumab effectively penetrates the retina and the

subretinal space after intravitreal injection.

Its systemic half-life is short (2-3 hours, following intravitreal administration) and systemic clearance is fast, which makes its administration safe.

The average vitreous elimination half-life is approximately10 days[42,43]. Ranibizumab has been approved for all types of exudative/neovascular AMD lesions: classic, predominantly classic, minimally classic and occult lesions with no classic component, up to 12 disc areas (DA), where the neovascular component is ≥ 50% of the entire lesion.

The recommended dose is 0.5 mg.

Treatment includes a loading phase, consisting of 3 monthly injections, in the first 3 months, and a maintenance phase, where retreatment is decided according to disease progression, mostly evaluated in monthly visits through VA and OCT criteria, at least during the initial stage or recent neovascularization activity[44].

Phase III clinical trials MARINA and ANCHOR, which supported ranibizumab approval for the treatment of AMD, demonstrated that treatment with monthly intravitreal injections for a 12 months period was associated with a significant increase in visual acuity, compared to photodynamic therapy and placebo[45].

After 12 months, 25-40% of patients treated with ranibizumab showed gains of ≥ 15 letters (ETDRS), compared to 5-6% of the control group patients ($p<0.001$).

Similar results were confirmed after 2 years.

Both these studies have established ranibizumab as the first therapy not only capable of preventing loss of vision but also of improving vision in a substantial percentage of patients: 33% of the patients treated with ranibizumab in the MARINA study and 41% in the ANCHOR study showed visual gains of at least 15 letters[45, 46,47,48, 49].

Subsequent studies (PIER, SUSTAIN, EXCITE) were aimed at defining flexible and individual dose regimes for the maintenance stage of treatment with ranibizumab, allowing an effective approach to maintaining visual gains, practical in terms of hospital follow-up and with maximum systemic and ocular safety[50,51,52].

These visual gains translate into real benefits for patients.

This effect was evaluated through 3 VFQ-25 sub-scales (near vision, distance vision and vision-related dependency); in fact, patients treated with ranibizumab showed improvements in these 3 sub-scales (MARINA and ANCHOR endpoints).

Specifically regarding dependency, ranibizumab allowed patients to become more independent in their daily activities.

Overall average VFQ scores increased by 4.6 points in the Lucentis® 0.5 group, compared to a 4.4-point decrease observed in the placebo group[53].

The PIER study evaluated an alternative therapeutic regime consisting of monthly injections, in the first 3 months, followed by quarterly injections, corresponding to a total of 6 injections within a year.

After an initial gain of 4.8 letters at month 3, patients treated with ranibizumab had lost an average of 0.2 letters at month 12, whereas patients in the control group lost 16.3 letters.

These results indicate that individual treatment criteria should be adopted during the maintenance stage, allowing an effective approach to maintaining visual gains, as well as allowing follow-up in clinical practice, with maximum systemic and ocular safety.

Vision is expected to be maintained in 90-95% of patients; a minimum gain of 3 lines should be observed in 30-40% of patients treated with ranibizumab[50].

In the EXCITE study, the quarterly treatment regime used in the PIER study (0.3 mg and 0.5 mg) was directly compared with a monthly regime (0.3 mg).

An average increase in VA was observed in all treatment groups during the 12 months of study duration. At month 12, compared to month 3, VA gains had decreased slightly with the quarterly regime (by -2.2 and -3.1 letters with ranibizumab 0.3 mg and 0.5 mg, respectively), having slightly increased (by +0.9 letters) with monthly administration of 0.3 mg of ranibizumab[52].

PrONTO, a small prospective, unicentric, open-label, non-randomized study sponsored by the investigator, evaluated the efficacy of 3 consecutive monthly injections, followed by individual retreatment based on OCT results (at intervals ≥ 1 month).

Retreatment criteria were: loss of 5 letters in VA, presence of fluid in the macula detected by OCT; increase ≥ 100 µm in central retinal thickness (CRT); de novo classic choroidal neovascularization; de novo macular haemorrhage; or persistent macular fluid detected by OCT.

Despite similar VA outcomes to those observed in the MARINA and ANCHOR studies having been observed with a smaller number of intravitreal injections, comparisons are limited by substantial differences in study design.

Although being a small, open-label trial, this study suggests that individual retreatment based on OCT results allows visual gains to be maintained with a smaller number of injections[45,54] .

The SAILOR-cohort 1 study evaluated the efficacy and safety of 3 consecutive monthly injections followed by quarterly monitoring visits, injections according to VA criteria (loss of > 5 letters from the maximum previous VA score) and OCT, if available (increase > 100 µm in CRT from the lowest previous measurement).

Additional visits/injections would take place if required.

Average VA increased from baseline after the first 3 injections, having subsequently decreased to an average gain of 2.3 letters for both ranibizumab doses, a better outcome than that observed for the PIER study, albeit suboptimal compared to those observed in the ANCHOR and MARINA studies.

These results indicate that quarterly visits are not sufficient to monitor and evaluate disease progression[45,55].

The objective of the SUSTAIN study was to evaluate the efficacy of 3 consecutive monthly injections followed by monthly monitoring and treatment according to the following criteria: loss of > 5 letters from the maximum previous VA score, in the first 3 months; or increase > 100 µm in CRT from the lowest previous measurement, in the first 3 months.

It was observed at month 12 that the majority of visual gains achieved in the first 3 months had been maintained.

Although this study consisted only of an interim analysis of 69 patients, the corresponding results suggest that efficacy outcomes may be maintained by a flexible regime with a smaller number of intravitreal injections and monthly monitoring.

However, some VA loss occurred after month 3, whereas fixed monthly injections led to additional VA gains during the maintenance stage[51,56].

In summary, the best VA outcomes were achieved with the monthly regime.

The poorest, albeit variable, efficacy outcomes were observed in studies with < 5 intravitreal injections.

The PrONTO and SUSTAIN studies demonstrated that monthly monitoring is required to maintain efficacy benefits, when compared to the SAILOR-cohort 1 study, which included compulsory quarterly monitoring visits, although more frequent follow-up was performed in many patients.

Therefore, ranibizumab emerges as the first approved neovascular AMD therapy (FDA approval in June 2006) able to improve visual acuity, having thus been recommended as first line therapy by many Ophthalmological Societies (e.g., the Royal College of Ophthalmologists, the German Ophthalmologists Association, etc.) and NICE (National Institute for Health and Clinical Excellence)[57].

Extension study HORIZON was performed in order to evaluate efficacy and safety after the first 2 years.

This study was designed as a post-marketing surveillance to monitor the safety and tolerability of Lucentis®, with a follow-up period of up to 3 years.

HORIZON enrolled 853 patients who had already completed one of the 2-year randomized Lucentis® trials, ANCHOR, MARINA or FOCUS[58,59].

While participating in the ANCHOR, MARINA or FOCUS studies, patients received monthly injections (active treatment with Lucentis® or Visudyne®, or sham).

During the HORIZON study, patients attended fixed quarterly visits; however, visit frequency could be increased by the investigator if they deemed it necessary to see the patient more often.

Lucentis® 0.5 mg injections were given on an as-needed basis, when the investigator felt that the patient would benefit from Lucentis® treatment.

The interval between injections was at least 30 days.

After 2 years (preliminary results), 69% of the 600 initial Lucentis®-treated patients received their injections.

Visual Acuity was available for 384/600 patients.

Among these 384 patients, median Snellen VA had increased by 3 lines, from 20/100 to 20/50, during the initial 2-year trial, having subsequently decreased by 2 lines from the HORIZON baseline to 20/80, at year 2 of the HORIZON study.

Overall, the safety profile of Lucentis® was very good and consistent with previous pivotal clinical trials of Lucentis®.

In general, better VA and anatomical outcomes after the first 2 years delayed the need for subsequent retreatment.

Additionally, the need for early AMD treatment was somewhat confirmed.

ome loss of previously achieved VA gains occurred, eventually related to sub-treatment during the extension period.

Loss of visual acuity and the need for retreatment during the HORIZON study shows that the disease remains active after the first two years of monthly injections, evidencing the need for careful patient monitoring, as well as timely retreatment.

In clinical trials, the benefits of ranibizumab regarding visual acuity were independent of the type of CNV lesion.

Additionally, these benefits were associated with a low rate (< 0.1%) of severe adverse events (endophthalmitis, retinal detachment, traumatic cataract).

Less severe ocular adverse events occurred in less than 2% of patients, including intraocular inflammation and increase in intraocular pressure. In all clinical trials, Lucentis® revealed to be a well-tolerated drug, with no statistically significant differences observed in ocular adverse events between treatment arms.

The results of the SAILOR study suggest a possible increase in the risk of de novo cardio vascular adverse events (CVA) in patients treated with ranibizumab with previous history of CVA or its risk factors (e.g., cardiac arrhythmias), although the differences observed were not statistically significant.

Safety monitoring during the post-marketing period has confirmed the good ocular and systemic safety profile of ranibizumab, whose risk management plan has been strictly implemented.

Other clinical trials are in course for other therapeutic indications, namely Diabetic Macular Oedema, Central Retinal Vein Occlusion and other ocular pathologies involving choroidal neovascularization, whose preliminary results have revealed to be promising.

Pegaptanib (Macugen®)

Pegaptanib sodium (Macugen®, OSI-Eyetech Pharmaceuticals, Pfizer), was the first anti-VEGF inhibitor available for the treatment of choroidal neovascularization[(60)].

This medicine is part of a new drug set called aptamers.

The aptamers are synthetic oligonucleotides which acquire a specific tridimensional shape and allow high specificity and affinity to a great extent of therapeutic agents.

These compounds are chemically synthetised with the use of nucleotide bases and the use of reverse transcription and PCR - polymerase chain reaction technology[(61)].

Pegaptanib sodium is a 28-base ribonucleic acid (RNA) oligonucleotide with two branched 20KDa polyethylene glycol (PEG) moieties attached in order to increase the half-life of the drug in the vitreous cavity.

The RNA sugar background is modified to prevent its degradation by endogenous endo and exo-nucleases[62].

Pegaptanib sodium specifically targets the VEGF165 isoform[63].

The pharmacokinetics of pegaptanib following intravitreous injection were profiled in a study of 147 subjects with exsudative AMD (Apte RS, 2007).

Either 1 or 3 mg of pegaptanib sodium per study eye was administered every 6 weeks for 54 weeks.

For the 1 mg dose, mean maximal plasma concentrations were 20 – 24 ng/ml, and pegaptanib was measurable (> 8 ng/ml) in the plasma for up to 1 week after injection.

The mean apparent terminal plasma half-life, determined from the 3 mg group, was 10 days.

There was no plasma accumulation with administration of repeated doses.

In addition, no serum antibodies against pegaptanib were detected[64, 65].

In monkeys' eyes, biologically active pegaptanib could be detected in the vitreous humor for at least 28 days, following a single 0.5 mg intravitreous injection dose[66].

Clinical trials with pegaptanib

Phases I and II studies

A phase IA safety study with 15 patients with exudative AMD(67), as well as a phase II study with 21 patients treated with pegaptanib associated or not to photodynamic treatment (PDT)[68], with a follow up of 3 months, have shown that the intravitreous administration of pegaptanib with 6 week intervals was well tolerated and had anatomic and visual benefits[69].

Phase III study

The study VISION (VEGF Inhibition Study in Ocular Neovascularization) consists of two multicentric, randomized, prospective, controlled, dose-ranging and double-blinded phase III clinical trials, used for testing the safety and efficiency of pegaptanib sodium in the treatment of choroidal neovascularization secondary to AMD[70].

There were 1208 patients in this study, distributed by 117 centers and the main criteria for inclusion were: 50-year old or above with any kind of angiographic subtype of subfoveal choroidal neovascularization in the study eye secondary to AMD, with a lesion of 12 or below disc areas (including blood, scarring, atrophy and neovascularization).

The best-corrected visual acuity varied between 20/320 and 20/40.

Patients were randomized in four branches of the study: a group for simulation of pegaptanib intravitreous injections and one of three groups for administration of pegaptanib sodium intravitreous injections (with doses of 0,3 mg, 1mg or 3 mg).

The injections (or simulations) were performed with 6-week intervals for 48 weeks, in a maximum of 8 injections per patient.

All patients underwent the same procedures with exception of the scleral penetration performed in the group of intravitreous injection simulation.

The ophthalmologist performing the injections was not authorized to undertake the patients' follow up in order to guarantee the researcher's concealment.

For ethical reasons, treatment with PDT (Visudyne®) was allowed in some clinical centers in patients with mainly classic lesions, in all branches of the study and according to the researcher's criteria.

The primary study outcome measure was the proportion of patients who lost <15 letters of VA at the end of week 54.

Additional efficacy end-points included: proportion of patients maintaining or gaining > 0, 5, 10, or 15 letters, or losing > 30 letters (severe vision loss); mean changes in VA from baseline to week 54, and the proportion of patients with VA of 20/200 or worse in the study eye at week 54.

In total, 1186 subjects received at least one study treatment (mean, 8.5 of 9 possible injections)[(61)].

All pegaptanib doses were superior to sham with regard to loss of < 15 letters of VA: 70, 71 and 65% for 0.3 mg ($p < 0.001$), 1 mg ($p < 0.001$) and 3 mg ($p < 0.03$) groups, respectively, versus 55% for sham.

Overall, the 0.3 mg dose was found to be most effective and further discussion is limited to the 0.3 mg (approved) dose.

Pegaptanib was significant superior to sham in the percentage of subjects maintaining or gaining 0, 5, 10 or 15 lines of vision ($p <0.05$)[(71)].

Pegaptanib treated subjects were less likely to have severe vision loss (10 versus 22%, $p < 0.001$) or progress to VA < 20/200 (38 versus 56%; < 0.001).

Mean VA loss at week 54 was 7.95 letters for pegaptanib compared with 15.05 letters for sham ($p < 0.05$; 47% relative difference).

Treatment effect was independent of angiographic subtype, baseline VA and lesion size, sex, age, race or iris color[(71)]. VISION trial had an extension for 48 additional weeks.

Those patients receiving pegaptanib were randomized to either continue their pegaptanib dose or discontinue treatment.

Subjects initially receiving sham were rerandomized to continue or discontinue sham or to receive one of the three pegaptanib doses.

Overall, 1053 subjects were rerandomized; 941 (89%) were assessed at week 102 (mean, 15.7 of 17 possible total injections).

Compared with sham (sham over 2 years or randomized to discontinue sham in year 2), more of those receiving pegaptanib 0.3 mg during 2 years lost < 15 letters (45 versus 59%; $p < 0.05$).

Subjects continuing pegaptanib had the greatest benefits[(72)].

An exploratory analysis was conducted to assess the vision benefit of treating early subfoveal choroidal neovascularization secondary to AMD with pegaptanib in the VISION trials.

Subjects were grouped according to two different definitions of early disease.

Group 1 included those with lesions < 2 disc areas and a baseline VA of ≥ 54 letters, no prior PDT or laser photocoagulation and scarring or atrophy (n = 34 for pegaptanib 0.3 mg and n = 28 for sham).

Group 2 included those with occult with no classic CNV, with an absence of lipid and worse VA in the study eye versus the fellow eye (n = 30 for pegaptanib 0.3 mg and n = 35 for sham)[(70)].

At week 54, the responder rates (lost < 15 letters) were significantly higher for pegaptanib versus sham (group 1: 76 versus 50%; $p = 0.03$; group 2: 80 versus 57%; $p = 0.05$).

Pegaptanib-treated subjects in group 1 were approximately 10-times less likely to have severe vision loss than those receiving sham (3 versus 29%; $p < 0.01$); differences for group 2 were not as large (10 versus 17%; $p = 0.17$).

On average, subjects in both pegaptanib-treated groups lost less VA (group 1: -5.6 versus -16.6 letters; $p < 0.01$; group 2: -4.0 versus -16.7 letters; $p < 0.006$).

Notably, among those receiving pegaptanib 0.3 mg 12% of subjects in group 1 and 20% in group 2 gained ≥ 3 lines of vision, compared with 6% in the VISION study.

These findings suggest that pegaptanib treatment early in the course of wet AMD may improve visual outcomes[(65, 70)].

Safety

During the VISION study and the second and third year extension no increased risk of systemic adverse

events was identified, but patients with high risk of cardiovascular and cerebrovascular events were excluded from the clinical trials.

Most adverse events reported in the study eyes were attributed to the injection procedure.

The low risk of serious injection-related adverse events, such as endophthalmitis, traumatic cataract and retinal detachment were found to be modifiable with injection protocols changes during the study (Table 1).

Event	Year 1 n = 7545 injections	Year 2 n = 4091 injections	Year 3 n = 3227 injections
Endophthalmitis	0.16	0.10	0.06
Traumatic cataract	0.07	0.02	0
Retinal detachment	0.08	0.17	0.03

Table 1 - VISION study serious ocular adverse events rates (% per injection)61. Adapted from Rajendra S Apte, 2008.

Because VEGF is involved in a wide range of physiological processes, inhibition of this factor raises many safety concerns particularly in the context of extended treatment regimens[(75-77)].

The pegaptanib sodium selectively inhibits the most biologically active isoform of VEGF (VEGF 165), and according to some authors this quality allows a theoretical advantage in terms of safety comparing to the non-selective anti-VEGF like ranibizumab and bevacizumab.

The systemic risks of non-selective VEGF inhibition have been illustrated with the use of intravenous injection of bevacizumab for the treatment of metastatic colorectal and non-small-cell lung cancer, both approved indications for this agent.

Nevertheless, the intravitreous administration of anti-VEGF agents for the treatment of exudative AMD results in much lower systemic exposures[(65)].

Although the theoretical superior safety of pegaptanip in comparison to other non-selective anti-VEGFs this has not been confirmed yet.

Bevacizumab (Avastin®)

Bevacizumab (Avastin®, Genentech, Roche) is a recombinant, humanized, monoclonal immunoglobulin G1 antibody (149 kD) that binds to and inhibits the biologic activity of all isoforms of human VEGF.

This molecule has 2 antigen-binding domains (ranibizumab has 1).

In 2004, the FDA approved bevacizumab for use in patients with metastatic colorectal cancer.

It has received additional approval for use in patients with non–small-cell lung cancer and those with metastatic breast cancer[(78-81)].

Though not formally studied or approved for any intraocular disease, Rosenfeld’s pioneering work and the unavailability of a related ocular drug, ranibizumab, led to rapid and wide use of bevacizumab all over the world[(82,83)].

Using bevacizumab as an intravitreal injection to treat neovascular AMD is off-label at this time, however many ophthalmologists, appropriately offer intravitreal bevacizumab to AMD patients based on multiple forms of evidence: results from several retrospective case series, extrapolation from the magnitude of the outcomes reported with ranibizumab, the structural similarity between ranibizumab and bevacizumab, the individual, and the natural history of the disease if left untreated[(84)].

In the human retina, it is unclear if the molecule of bevacizumab fully distributes within the retinal layers or if localized inhibition of VEGF in the vitreous and inner retina is responsible for the clinical effects associated with administration[(85-87)].

There are also theories that the larger size of bevacizumab relative to ranibizumab may result in bevacizumab not clearing as quickly from the eye, potentially resulting in longer duration of activity.

To the knowledge of this author, this claim has not been confirmed[(84)].

Full antibodies generally have longer systemic half-lives than antibody fragments.

Therefore, it is assumed that the half-life of bevacizumab in the eye and in the circulation is longer than that of ranibizumab after intravitreal injection.

Different half-lives for these 2 drugs may have implications for different dosing frequencies and different systemic toxicities[(78,86-91).]

Experimental and clinical studies

Following the initial successful administration of this drug in the management of exudative AMD in May 2005, numerous case series were published illustrating the effectiveness of this treatment in a high proportion of patients[(92)].

Almost all of the evidence supporting the use on neovascular AMD comes from off-label usage in short-term uncontrolled clinical case series, which suggests that intravitreal administration is apparently locally and systemically well tolerated and is associated with vision stabilization or improvement in most treated eyes[(85,86,87,91,94)].

One of the earlier large retrospective case series in the literature included 81 consecutive eyes (79 patients) with subfoveal choroidal neovascularization treated with 1.25 mg (0.05 cc) intravitreal bevacizumab, at baseline and 1 month later if morphologic changes attributable to the CNV persisted (subretinal fluid, pigment epithelial detachment, retinal thickening).

Seventy-eight percent had prior treatment with pegaptanib, photodynamic therapy (PDT), or both.

After one IVB injection, 30 of 81 eyes had resolution of their subretinal fluid. At 2 months, 50% demonstrated resolution of leakage.

The mean best corrected visual acuity (BCVA) improved from 20/200 to 20/125 at week 8 ($p < 0.0001$)[(91)].

Spaide et al. in a subsequent study evaluated 266 eyes, 70% of which had prior treatment for exudative AMD (PDT or pegaptanib).

At the 3-month follow-up (data available for 141 patients) 38.3% patients improved by 2 or more Snellen lines.

Mean BCVA improved from 20/184 to 20/109 at 3 months ($p<0.001$).

Central retinal thickness measured by OCT improved over 3 months from a mean of 340 microns to a mean of 213 microns ($p<0.001$)[(95)].

A greater visual acuity effect has been reported in naïve eyes compared to those that have received previous treatment, for example in a study of 50 eyes (48 patients) treated with bevacizumab for exudative AMD found that naïve eyes responded more favorably than previously treated eyes.

Six of the 14 (43%) of naïve eyes gained 3 lines or more of vision versus 17% of eyes that had undergone prior treatment.

The naïve group’s mean visual acuity improved from 20/160 at baseline to 20/63 ($p<0.001$) at week 24[(96)].

Such visual acuity gains were not reported with PDT or pegaptanib treatment and were comparable to the results of the phase III studies of ranibizumab.

However, those with longstanding exudative AMD have also been shown to improve with treatment.

One retrospective study in 48 eyes with exudative AMD for 5 months or longer (mean 17.9 months) showed that 25% of those improved at least 3 lines with bevacizumab intravitreous injection after a mean follow-up of 27 weeks[(96)].

In another prospective case series, Bashshur et al. injected 2.5 mg (0.1ml) of bevacizumab (twice the dose most frequently used) into the vitreous in 17 eyes with wet AMD patients and followed by two additional injections at four-week intervals.

Mean best-corrected visual acuity was 20/252 at baseline and 20/76 at week 12 ($P < 0.001$).

Mean central subfield retinal thickness also improved between baseline and week 12 in all 17 patients.

No systemic or ocular side effects were noted[(85)].

Safety

Data on the safety of intravitreal bevacizumab are more limited than data on ranibizumab or pegaptanib safety because there are no large, prospective, controlled safety studies with this treatment.

Local side-effects are similar to those found for the other anti-VEGF agents[(98)].

A safety retrospective study evaluating the side effects of intravitreal bevacizumab reviewed 1265 patients for 12 months, with 92 lost to follow-up.

Ocular complications included seven (0.16%) bacterial endophthalmitis, seven (0.16%) tractional retinal detachments, four (0.09%) uveitis, and a case (0.02%) of rhegmatogenous retinal detachment and another case (0.02%) of retinal detachment and vitreous hemorrhage[(99)].

In electrophysiological studies no negative side-effects were seen on the retina. In contrast, the results showed a recovery effect on photoreceptors even at the site of the CNV(100).

Most of the in vitro, ex vivo and in vivo experiments excluded short-term negative effects on ocular cells and histology[(101,102,103,104,105)].

A paper, however, discloses mitochondrial disruption in the inner segment of photoreceptors and apoptosis after high doses of intravitreal bevacizumab in the rabbit eye.

The electrophysiological investigation and light microscopy, in contrast appeared unaltered.

This suggests that potential side-effects on the cellular level cannot be detected with the present diagnostic tools in clinical practice[(98,106)].

Intravenous use of bevacizumab in patients with colorectal cancer is associated with severe systemic side effects including arterial thromboembolism, gastrointestinal perforation, hemorrhage, hypertensive crisis and nephrotic syndrome.

Initial studies using this therapy intravenously for ocular disease in a healthier population did not find nearly the same risks[(107,108)].

The dose of intravitreal bevacizumab is much lower (1/400th) of the dose used for intravenous treatment and has not been found to result in unexpected systemic side effects[(92)].

There are no studies adequately undertaken to identify rare systemic events.

In a 3-month retrospective study of bevacizumab treatment in 266 patients, 1 (0.4%) developed a nonfatal myocardial infarction after the third injection.

Two patients (0.8%) had apparent transient ischemic attacks (diagnosis was not definitive).

There were 2 deaths, one from myocardial infarction.

Nevertheless, that patient was a smoker with a history of emphysema.

It is important to consider, however, that this population (mean age, 80.3 years) is at risk for myocardial infraction regardless of treatment.

Any potential safety concerns remain unknown and waiting for randomized and controlled clinical trials.

Discussion

The initial results of intravitreal bevacizumab for exudative AMD led to the acceptance of this off-label therapy by ophthalmologists around the world, assuming, based on case series evidence, that bevacizumab is at least almost as good as ranibizumab with respect to efficacy and safety.

Some ophthalmologists might recommend bevacizumab instead of ranibizumab, even when it is available and affordable to the patient, because of the concerns regarding the treatment costs[84,92].

Intravitreal bevacizumab accounts for more than 50% of all anti-VEGF therapy delivered for exudative AMD in the United States[109].

The National Eye Institute is sponsoring a clinical trial to compare the safety and efficacy betwen bevacizumab and ranibizumab for the treatment of exudative AMD – CATT study.

This study and other prospective, controlled and randomized trials in several countries (IVAN-UK, VIBERA-Germany, MANTA-Austria, LUCAS-Norway, GEFAL-France) will provide the best level of evidence regarding the efficacy and safety of bevacizumab.

Some of these ongoing studies can give consistent information about the necessary dose-ranging and dosing-frequency to control AMD neovascularization.

Nice recommendations(57) (National Institute for Health and Clinical Excellence; April 2008)

According to NICE, ranibizumab is the only anti-VEGF recommended for the treatment of Age-related Macular Degeneration (as per the NICE Guidelines, published in 2008).

Differences are clear when comparing the outcomes of clinical programs for both drugs (ranibizumab and pegaptanib).

In clinical trials with ranibizumab, the percentage of patients who gained 15 letters or more was substantially higher, whereas in clinical trials with pegaptanib few patients gained 15 letters or more compared to the control group.

Regarding visual acuity outcomes (expressed as the average number of letters lost or gained by both treatment groups versus the control group), the observed results revealed that ranibizumab leads to statistically significant average gains, whereas pegaptanib only leads to a decrease in the average loss, i.e., ranibizumab is more effective than pegaptanib regarding improvements in visual acuity.

Additionally, no benefits were observed in patients whose treatment with pegaptanib was discontinued after the first year, when compared to patients in the placebo group (VISION study results, published in 2006).

According to NICE, both drugs (ranibizumab and pegaptanib) have demonstrated clinical efficacy in the treatment of exudative AMD, although ranibizumab leads to increased clinical benefits and pegaptanib fails to represent a cost-effective example of healthcare resource use, thus not being recommended in the treatment of AMD.

On the contrary, ranibizumab is referred as an option in the treatment of this condition, providing the following are observed for the treated eye:

- visual acuity between 6/12 and 6/96
- no permanent structural damage to the central fovea
- lesion size less than or equal to 12 disc areas in its greatest linear dimension
- evidence of recent disease progression (vessel pro liferation, observed in fluorescein angiography, or recent changes in visual acuity).

>> References

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