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Review Article

Development of Anti-VEGF Therapies for Intraocular Use: A Guide for Clinicians

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Angiogenesis is the process by which new blood vessels form from existing vessel networks. In the past three decades, significant progress has been made in our understanding of angiogenesis; progress driven in large part by the increasing realization that blood vessel growth can promote or facilitate disease. By the early 1990s, it had become clear that the recently discovered "vascular endothelial growth factor" (VEGF) was a powerful mediator of angiogenesis. As a result, several groups targeted this molecule as a potential mediator of retinal ischemia-induced neovascularization in disorders such as diabetic retinopathy and retinal vein occlusion. Around this time, it also became clear that increased intraocular VEGF production was not limited to ischemic retinal diseases but was also a feature of choroidal vascular diseases such as neovascular age-related macular degeneration (AMD). Thus, a new therapeutic era emerged, utilizing VEGF blockade for the management of chorioretinal diseases characterized by vascular hyperpermeability and/or neovascularization. In this review, we provide a guide for clinicians on the development of anti-VEGF therapies for intraocular use.

1. Introduction

In 1948, Isaac Michaelson proposed that a diffusible factor (named afterward "factor X") could be responsible, not only for the development of the normal retinal vasculature but also for pathological neovascularization in proliferative diabetic retinopathy and other ocular disorders [1]. By the early 1990s, it had become clear that the recently discovered "vascular endothelial growth factor" (VEGF) possessed many of the requisite characteristics of a "factor X" [2]. As a result, several groups targeted this molecule as a potential mediator of retinal ischemia-induced neovascularization in disorders such as diabetic retinopathy and retinal vein occlusion (RVO) [3, 4]. Around this time, it also became clear that increased intraocular VEGF production was not limited to ischemic retinal diseases but was also a feature of choroidal vascular diseases such as neovascular age-related macular degeneration (AMD) [5, 6]. Thus, a new therapeutic era emerged, utilizing VEGF blockade for the management of chorioretinal diseases characterized by vascular hyperpermeability and/or neovascularization.

In this review, we begin by providing an overview of angiogenesis, the manner in which VEGF was discovered to be central to this process, and then a summary of VEGF biology. In this manner, we aim to provide the clinician with an understanding of the clinical scenarios in which VEGF blockade is likely to be successful and of patient benefit. We continue by describing the development of four key anti-VEGF therapies (pegaptanib, bevacizumab, ranibizumab, and aflibercept) and the results of their application in a selection of pioneering clinical trials. By describing the main features of their development in a manner accessible to clinicians, we aim to highlight those molecular characteristics, of each agent, with implications for clinical outcomes and patient safety. We conclude the review by describing likely future directions in the application of anti-VEGF therapy in chorioretinal disease.

2. Angiogenesis

2.1. Overview. Angiogenesis is the process by which new blood vessels form from existing vessel networks (by comparison, vasculogenesis is a form of de novo blood vessel formation that is typically seen in the embryo) [7–9]. Angiogenesis begins with vasodilatation and increases in vascular permeability, followed by activation and proliferation of vascular endothelial cells; these changes are accompanied by degradation of the surrounding extracellular matrix (ECM), facilitating endothelial cell migration. The migrating endothelial cells assemble, form cords, and ultimately acquire lumens; further differentiation to accommodate local requirements then occurs and a network of similarly differentiated periendothelial cells and matrix develops. After further remodeling a complex vascular network is ultimately formed.

2.2. Role of Angiogenesis in Disease. In the past three decades, significant progress has been made in our understanding of angiogenesis: progress driven in large part by the increasing realization that blood vessel growth can promote or facilitate disease [10]. This major conceptual advance first occurred in the 1930s and 1940s, when it was hypothesized that induction of blood vessel growth through release of vasoproliferative factors would confer a growth advantage on tumor cells [11]. Subsequently, in the 1970s, Folkman hypothesized that blockade of angiogenesis could be a strategy to treat cancer and other disorders [12]. However, adoption of such a strategy first required the identification and characterization of the mediators of angiogenesis—a major technological challenge at that point.

2.3. Putative Regulators of Angiogenesis. In the subsequent years, advances in molecular biology led to the identification of many putative regulators of angiogenesis, with well-known examples including basic fibroblast growth factor (bFGF), transforming growth factor (TGF)-β, and the angiopoietins [7]. In the 1980s, bFGF was thought to be the major angiogenic factor in the pituitary and other organs. However, this model was called into question when, in 1986, it became clear that bFGF lacks a peptide sequence necessary for secretion and is thus confined intracellularly (angiogenesis is a process that requires diffusion in an extracellular environment) [13].

2.4. Discovery of VEGF. In the mid-1980s, Ferrara and Henzel cultured a population of nonhormone secreting follicular cells—with unusual characteristics—from bovine pituitary glands (follicular cells have cytoplasmic projections that establish intimate connections with perivascular spaces and were thought to have a role in regulating growth and maintenance of pituitary vasculature) [14]. Ferrara discovered that culture medium conditioned by these cells strongly promoted endothelial cell growth. He hypothesized that this mitogenic activity may be the result of a secreted protein; the subsequent isolation and sequencing of this protein led to discovery of the most important mediator of angiogenesis currently known—VEGF [15].

2.5. Vascular Permeability Factor. Independently, in the early 1980s, Senger et al. had reported the identification of a permeability-enhancing protein (in the supernatant of a guinea pig tumor cell line), which they named "vascular permeability factor" (VPF) [16]. In 1989, at the same time Ferrara and coworkers were reported their discovery of VEGF. Keck et al. reported the isolation and sequencing of VPF [17]. Surprisingly, their findings indicated that VEGF and VPF were, in fact, the same molecule.

2.6. Clinical Role for VEGF Blockade. Although multiple growth factors other than VEGF have been implicated in the angiogenic process (e.g., bFGF), VEGF appears critical for a number of reasons: its production is driven by hypoxia; it is highly selective for endothelial cells, it possesses diffusion characteristics that allow it to reach its target, and it affects multiple aspects of the angiogenic process [18, 19]. VEGF also causes vascular dilatation and promotes vasopermeability, both of which facilitate a rich environment for the growth of new vessels. Thus, despite the complexity of the angiogenic process, and the potential redundancy of the growth factors involved, VEGF blockade was quickly recognized as a promising approach for the restriction of blood vessel formation in a variety of pathologic scenarios [8].

3. VEGF Biology

3.1. Gene Family. VEGF-A, first discovered in 1989 (see above), is the prototype member of a gene family (i.e., a group of genes with shared sequences and with similar biochemical functions) that also includes placental growth factor (PLGF), VEGF-B, VEGF-C, VEGF-D, and VEGF-E (prior to the discovery of other family members, VEGF-A was known simply as VEGF; the terms are used interchangeably in this review) [10, 18]. Of note, VEGF-C and VEGF-D are involved in the regulation of lymphatic angiogenesis [20], demonstrating the unique role of this gene family in controlling multiple structural components of the vascular system.

3.2. Regulation of VEGF Gene Expression. Oxygen tension has a key role in regulating the production of VEGF. VEGF mRNA expression is induced by exposure to low oxygen tension under a variety of pathophysiological circumstances, and it is now well established that a transcription factor, hypoxia-inducible factor-1 (HIF-1), is a key mediator of this response [21, 22]. Recent studies have also shown that Von Hippel Lindau (VHL) protein, a product of the VHL tumor suppressor gene, provides negative regulation of VEGF and other hypoxia-inducible genes (inactivation of this gene leads to development of capillary hemangioblastomas in the retina and cerebellum, and in many cases, renal cell carcinomas) [23].

Several major growth factors, such as epidermal growth factor, also upregulate VEGF mRNA expression, suggesting that paracrine or autocrine release of such factors works in concert with local hypoxia to increase production of VEGF [24, 25]. In addition, inflammatory cytokines, such as

interleukin-1α and interleukin-6, induce expression of VEGF in several cell types (an observation in agreement with the hypothesis that VEGF plays a role in the angiogenesis and hyperpermeability seen in some inflammatory disorders) [25].

3.3. VEGF Isoforms. The human *VEGFA* gene is organized as eight exons separated by seven introns (i.e., eight expressed regions that are joined together in the final mature RNA) [26]. Alternative splicing of the *VEGFA* gene results in the generation of four major isoforms ($VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$, and $VEGF_{206}$), having, respectively 121, 165, 189, and 206 amino acids. $VEGF_{165}$ is the predominant isoform [27].

Native VEGF is a heparin-binding glycoprotein (heparin is commonly used during protein purification due to its structural similarity to RNA and DNA), with a protein molecular weight of 45 kDa, the properties of which correspond closely to those of $VEGF_{165}$ [27]. Loss of the heparin-binding domain of VEGF results in a significant loss in its mitogenic activity [28]. $VEGF_{121}$, while freely diffusible in the ECM, is acidic and does not bind heparin [27]. Conversely, $VEGF_{189}$ and $VEGF_{206}$, while being highly basic and capable of binding heparin with high affinity, are almost completely sequestered in the ECM. Thus, $VEGF_{165}$, with intermediary properties, possesses the optimal characteristics of bioavailability and biological potency [27].

3.4. VEGF Receptors. VEGF binds to two, related, receptor tyrosine kinases: VEGF Receptor 1 (VEGFR1) and VEGF Receptor 2 (VEGFR2) [27]. Both VEGFR1 and VEGFR2 have seven immunoglobulin-like domains in the ECM, a single transmembrane region, and a tyrosine kinase sequence interrupted by a kinase-insert domain. In 1992, VEGFR1 was the first VEGF receptor discovered and was found to bind VEGF with high affinity [29]. However, despite its lower binding affinity for VEGF relative to VEGFR1, there is now agreement that VEGFR2 is the major mediator of the mitogenic, angiogenic, and permeability-enhancing effects of VEGF (the precise function of VEGFR1 is still under debate but may provide a "decoy effect" on VEGF signaling) [27]. In addition, VEGF interacts with a family of nonsignaling coreceptors, the neuropilins—neuropilin-1 (NRP-1) appears to present $VEGF_{165}$ to VEGFR2 in a configuration that increases the effectiveness of VEGFR2-mediated signal transduction [18, 30].

3.5. Activities of VEGF. Vascular endothelial cells are the primary targets for VEGF biologic activity, with their mitogenic effects well documented, both *in vitro* and *in vivo* [27]. In particular VEGF induces a potent angiogenic effect in a variety of animal models *in vivo* [15, 31].

VEGF also acts as a survival factor for endothelial cells in a variety of circumstances. Inhibition of VEGF results in extensive apoptotic changes in the vasculature of neonatal, but not adult mice [32]; furthermore, a marked VEGF dependence has been demonstrated in the endothelial cells of newly formed but not of established vessels within tumors [33]. Coverage by pericytes is thought to be one of the key events, resulting in loss of VEGF dependence [34].

VEGF has also been shown to act as a chemotactic agent for bone marrow-derived monocytes [35], a pro-inflammatory cytokine through upregulation of intercellular adhesion molecule-1 (ICAM-1) with consequent leukocyte adhesion [36], and a promoter of blood vessel extravasation through the upregulation of matrix metalloproteinases and decreased release of metalloproteinase inhibitors [37].

The effects of VEGF on the promotion of vascular leakage, both in inflammation and in other pathologic circumstances, are also well established (prior to its isolation and sequencing, VEGF was initially characterized as "vascular permeability factor" by Senger et al. (see above)) [16]. Consistent with this role, VEGF has been shown to promote dissolution of tight junctions between endothelial cells and to induce endothelial fenestration in a number of vascular beds [38]. VEGF also induces vasodilatation in a dose-dependent fashion as a result of release of endothelial cell-derived nitric oxide—systemic blockade of VEGF may thus result in a clinically significant adverse hypertensive effect [39].

Taken together, blockade of the biologic effects of VEGF results in rapid vessel remodeling with regression of pericyte-poor capillaries, reductions in vascular lumen diameter, and reductions in vascular permeability [33, 34]. More recently, evidence has suggested that VEGF could have additional neuroprotective effects [40].

3.6. Role of VEGF in Ocular Disease. In 1994, Aiello et al. found a striking correlation between intraocular VEGF concentrations and active proliferative retinopathy in patients with diabetes and ischemic central retinal vein occlusion (CRVO) [3]. Around the same time, Adamis et al. reported increased concentrations of VEGF in the vitreous of patients with diabetic retinopathy [4]. In 1996, it also became clear that increased intraocular levels of VEGF were not limited to ischemic retinal disorders: in a pair of influential studies, the localization of VEGF to choroidal neovascular membranes in patients with neovascular AMD was reported [5, 6]. Proof-of-concept studies then demonstrated that blockade of VEGF, in animal models, led to marked decreases in retinal and iris neovascularization [41, 42]. Furthermore, exogenous administration of VEGF was demonstrated to produce retinal ischemia and vascular hyperpermeability in primates [43].

4. Pegaptanib

Pegaptanib sodium is an RNA aptamer that binds to the heparin-binding domain of VEGF and, thus, prevents the predominant $VEGF_{165}$ isoform from binding to VEGF receptors [44]. Pegaptanib was licensed to EyeTech Pharmaceuticals (now OSI Pharmaceuticals) for late stage development and marketing in the United States as "Macugen" (outside the USA, pegaptanib is marketed by Pfizer Inc.).

4.1. Chemistry. Aptamers (from the Latin *aptus,* to fit, and the Greek *meros,* part or region) are oligonucleotides that bind to specific target molecules and that are usually created

by selection from a large random sequence pool [45]. In this manner, aptamers are commonly used for basic research and clinical purposes as macromolecular drugs. Aptamers constitute one of four classes of oligonucleotide reagents, the others being antisense oligonucleotides, ribozymes, and small interfering RNAs (siRNAs) [44]. However, in contrast with these other entities, aptamers can act on extracellular targets and, therefore, are not required to cross cell membranes to exert their therapeutic effects.

The selection of aptamers has become relatively straightforward with the advent of "systematic evolution of ligands by exponential enrichment" (SELEX) [46]; in this process, aptamers are engineered to bind to various target molecules through repeated rounds of *in vitro* selection. Aptamers offer molecular recognition properties that rival that of antibodies, but with a number of advantages: (1) they can be engineered completely *in vitro*, (2) they are readily produced by chemical synthesis, (3) they possess desirable storage properties, and (4) they elicit little or no immunogenicity [44, 45]. Pegaptanib has the distinction of being the first aptamer therapeutic approved for use in humans [44].

Having chosen $VEGF_{165}$ as the target for selection of a prospective anti-VEGF aptamer, three separate iterations of the SELEX methodology were carried out by scientists at NeXstar Pharmaceuticals [44]. By 1998, three, stable, high-affinity anti-$VEGF_{165}$ aptamers had been characterized, one of which was selected for development as pegaptanib (initially designated NX1838, and then, EYE001) (all three aptamers demonstrated little or no binding to $VEGF_{121}$) [47].

4.2. Preclinical Studies. The fact that pegaptanib offers selective inhibition of a single isoform offers the theoretical advantage that "normal" vessels may be maintained by $VEGF_{121}$ and other isoforms, while pathologic neovascularization may be suppressed [18, 44, 48]. Indeed, prior to clinical trials in humans, basic research demonstrated that administration of EYE001 (pegaptanib) could lead to both reduced vascular permeability and inhibition of both corneal and retinal neovascularization [49]. It has subsequently been shown, however, that various proteases activated during angiogenesis may cleave $VEGF_{165}$ (and longer isoforms) to generate nonheparin binding fragments—such fragments may be sufficient to drive angiogenesis while evading pegaptanib blockade [50, 51].

4.3. Pharmacokinetics and Metabolism. Nonmodified aptamers are rapidly cleared from the body, with a half-life of minutes to hours, as a result of nuclease degradation and renal clearance (a result of the inherently low molecular weight of aptamers). Therefore, modification of aptamers, such as 2′-fluorine-substituted pyrimidines, and polyethylene glycol (PEG) linkage, can be used to increase their stability and terminal half-life (both approaches are used in the case of pegaptanib) [44]. Using these approaches pegaptanib has been found to be stable in human plasma, at ambient temperatures, for more than 18 hours [52].

Pegaptanib pharmacokinetics have been evaluated following intravitreal injection in monkeys and rabbits [49, 52, 53]. In both animal models, pegaptanib was detected in the vitreous at biologically active levels for at least 28 days following a single 0.5 mg intravitreal injection. In rabbits, after a single dose of pegaptanib, the initial vitreous humor levels were approximately 350 μg/mL and decreased by an apparent first-order elimination process to approximately 1.7 μg/mL by day 28. By comparison, the plasma concentrations of pegaptanib were significantly lower, ranging from 0.092 μg/mL to 0.005 μg/mL (day 1 to day 21). Plasma levels also declined by an apparent first-order elimination. In a human pharmacokinetic study, pegaptanib was not found to accumulate in the plasma after multiple doses (i.e., systemic exposures were similar at different time-points); furthermore, no antipegaptanib antibodies (IgG or IgM) were detected [54].

4.4. Selected Clinical Studies: Neovascular AMD. In 2004, following publication of results from two, concurrent, phase III clinical trials (the VEGF Inhibition Study in Ocular Neovascularization, or VISION, trials), pegaptanib was licensed for use in the USA by the Food and Drug Administration (FDA) [55]. The VISION trials—two large-scale, multicenter, randomized, controlled, clinical trials—demonstrated that intravitreal administration of 0.3 mg of pegaptanib at six weekly intervals, for a period of 48 weeks (a total of nine treatments), was effective in reducing moderate vision loss in patients with neovascular AMD (higher doses were not shown to provide clinical benefit). In these studies, 70% of pegaptanib-treated patients avoided further moderate visual loss (defined in most AMD studies as a loss of fewer than 15 letters of visual acuity) compared with 55% of sham-treated patients. However, treated eyes still lost, on average, 1.5 lines of visual acuity over the course of a year of treatment. There was no evidence of either systemic toxicity or an increased risk of potential VEGF inhibition-related adverse events (a safety profile confirmed following three years of treatment/follow-up) [56].

4.5. Selected Clinical Studies: Diabetic Macular Edema. In 2011, the results of a phase II/III-randomized controlled trial, of intravitreal pegaptanib for the treatment of diabetic macular edema (DME), were published [57]. In this study, subjects with DME received injections of 0.3 mg of intravitreal pegaptanib, or sham injections, every six weeks for a year, and then according to prespecified criteria in a second year. In all, 36.8% of patients receiving pegaptanib, versus 19.7% of those in the sham group, experienced an improvement in visual acuity greater than 10 letters when compared to baseline. After two years, pegaptanib-treated patients gained, on average, 6.1 letters of visual acuity (versus 1.3 letters for controls). Pegaptanib-treated patients also received fewer focal/grid laser treatments (subjects were eligible for this beginning at week 18).

5. Bevacizumab

Bevacizumab (Avastin, Genentech, South San Francisco, CA) is a full-length monoclonal antibody, first derived from a murine source and prepared for intravenous administration,

which binds to and inhibits all isoforms of VEGF [18, 58]. Bevacizumab was originally developed and approved for the treatment of metastatic colorectal cancer but may also be of benefit in the treatment of nonsmall cell lung cancer, metastatic breast cancer, and glioblastoma multiforme [59]. Use of bevacizumab in these contexts has been associated with increased incidences of hypertension, bleeding, and thromboembolic events [59]. However the doses employed for intraocular use are many times lower than those used systemically, and the efficacy and safety of bevacizumab, for the treatment of neovascular AMD, has recently been demonstrated in phase III clinical trials [60, 61].

5.1. Chemistry. Bevacizumab was originally developed from a mouse antihuman VEGF antibody (A.4.6.1), generated from mice immunized with the $VEGF_{165}$ isoform [58]. A.4.6.1 recognizes all isoforms of VEGF and, in 1992, was shown to inhibit growth of human tumor cell lines *in vivo* [62]. Subsequently, in 1996, intraocular administration of A.4.6.1 was found to inhibit iris neovascularization occurring secondary to retinal ischaemia in a primate model [42]. In 1997, bevacizumab was developed by humanization of A.4.6.1 [63]. In this process, six complementarity-determining regions (CDRs) (i.e., regions that determine antibody-binding) were transferred from A.4.6.1 to a human antibody framework previously used for humanizations. However, this transfer reduced VEGF binding over 1000 fold—to reduce this effect, eight framework residues were changed from human to murine.

Bevacizumab is produced in Chinese hamster ovary cells using expression plasmids (plasmids are DNA molecules separate from chromosomal DNA that can be used to manufacture large quantities of proteins) [58]. Bevacizumab is a 149 kDa full-length antibody, composed of two light chains and two heavy chains, and with a 93% human amino acid sequence.

5.2. Preclinical Studies. The effects of bevacizumab have been examined in a number of *in vitro* and *in vivo* studies [58]; as bevacizumab was not developed with the intention of intraocular administration, many of these studies were performed only after its widespread adoption in this manner for clinical practice. In both murine and porcine models, bevacizumab has been demonstrated to reduce VEGF-induced permeability and proliferation of choroidal endothelial cells and to inhibit VEGF-induced migration of human umbilical vein endothelial cells [64–66]. In addition, bevacizumab has been demonstrated as nontoxic, or not to alter the viability of, neurosensory retinal cells, retinal ganglion cells, and human retinal pigment epithelium (RPE) cells [58]. Concern has also been raised about the Fc component present in full-length antibodies such as bevacizumab—Fc domains are known to initiate complement activation and immune cell destruction [18]. Recent studies have demonstrated that choroidal neovascular membranes from patients with neovascular AMD treated with bevacizumab are characterized by significantly higher inflammatory activity [67]. Preliminary results have also demonstrated that bevacizumab Fc domains are capable of binding effectively to human RPE and human umbilical vascular endothelial cell (HUVEC) membranes via Fc receptors, activating the complement cascade and leading to cell death [58].

5.3. Pharmacokinetics and Metabolism. Bevacizumab was developed for intravenous administration in diseases such as colorectal cancer [59]. As a result, compounding into smaller doses is required for intraocular administration. Studies have demonstrated differences in bevacizumab concentration and the presence of particulate contaminants following this process, emphasizing the need for implementation of optimal protocols when compounding pharmacies prepare this drug for intravitreal use [58, 68].

The pharmacokinetics of bevacizumab, following intravitreal administration, have not been well characterized. Knowledge of the vitreous half-life is an important consideration when optimizing retreatment frequencies, whereas serum concentrations are an important factor with respect to systemic adverse effects (e.g., stroke). In rabbits receiving 1.25 mg of bevacizumab, the vitreous half-life was 4.32 days (versus 2.88 days for ranibizumab), and the maximum serum concentrations were reached after eight days [69, 70]. Small amounts of bevacizumab were also detected in the vitreous of the fellow, uninjected eye. In a more recent study performed in humans, an aqueous half-life of 9.82 days was found after intravitreal injection of 1.5 mg of bevacizumab [71].

The retinal penetration of bevacizumab has also been studied in animal models (experience with retinal penetration of other, full-length antibodies suggested that their large size would act as a limiting factor). In rabbits, Shahar et al. demonstrated, using confocal immunohistochemistry, that full thickness retinal penetration occurred 24 hours after intravitreal injection; this study also demonstrated the essential absence of bevacizumab from the retina by four weeks post injection [72].

5.4. Selected Clinical Studies: Neovascular AMD. In 2010, the results of the ABC (Avastin (Bevacizumab) for treatment of Choroidal Neovascularization) trial provided the first evidence from a phase III-randomized controlled study for the efficacy of intravitreal bevacizumab in neovascular AMD [60, 73]. In this single year trial, 32% of patients treated with bevacizumab gained 15 or more letters from baseline visual acuity (initial three month loading phase, and then retreatment as required). In addition, 91% of patients receiving bevacizumab lost fewer than 15 letters of visual acuity from baseline, and mean visual acuity increased by 7.0 letters over the study period.

In 2011, the results of the CATT (Comparison of Age-Related Macular Degeneration Treatments Trials) study provided further evidence, from larger phase III trial, for the efficacy of bevacizumab in neovascular AMD [61]. In this trial, 31.3% of patients treated with bevacizumab on a fixed, monthly regimen gained 15 or more letters from baseline visual acuity (28.0% for patients treated with bevacizumab as required). In addition, 94.0% of patients receiving bevacizumab on a fixed, monthly regimen lost fewer than 15 letters of visual acuity from baseline (91.5% in the bevacizumab as required group). Finally, mean visual acuity

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