Intravitreal Pharmacotherapy in Retinal Diseases

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Intravitreal drug delivery has become a popular method of treatment of many retinal and choroidal pathologies. The management of various retinal pathologies notably neovascular ARMD, diabetic macular edema and macular edema due to vein occlusions have undergone a sea change with the introduction of intravitreal steroids and anti VEGF therapy. Various multicentric trials have established the supremacy of these agents in clinical practice. Though very effective these intravitreal agents should be used very judiciously in clinical practice because of the risk of complications both ocular and systemic as in certain situations. In our setting it is best that these drugs are given in a sterile setting (preferably in the OR) after obtaining an informed consent. The aim of this article is to discuss the basis and role of intravitreal steroids and anti VEGF therapy in our clinical practise.

Intravitreal Steroids

In the past 10 years, intravitreal corticosteroid injection has emerged as an increasingly used treatment option for patients with a variety of posterior segment diseases, including diabetic macular edema (DME), branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), pseudophakic cystoid macular edema (CME), and uveitic macular edema (ME). Intravitreal steroids were initially considered after animal studies showed that dexamethasone phosphate injected into the vitreous cavity was not toxic to the retina. Then, attention was directed to triamcinolone acetonide (TA) for possible treatment of proliferative vitreoretinopathy because of its long duration of action and lack of retinal toxicity. Shortly after came the first published reports of human intravitreal injection of steroids, used for the treatment of DME in 2001 and for ME secondary to CRVO in 2002. Intravitreal delivery of steroids has allowed many posterior segment diseases to be treated locally without the systemic side effects of oral steroids. Intravitreal delivery also allows the steroid to bypass the blood–retina barrier (BRB), leading to a more concentrated dose of the steroid for a prolonged period of time. Delivery of the steroids into the vitreous cavity can be achieved by direct injection through the pars plana, introduction of a sustained release implant or injection of conjugate compounds.

Mechanism of Action

It is generally believed that corticosteroids have antiinflammatory, antipermeability, and anti-angiogenic properties. Corticosteroids have been shown to stabilize the BRB and improve ME, but the exact mechanism of action remains unclear. To date, there have been 2 major hypotheses for the mechanism of intravitreal corticosteroid action in BRB breakdown: (i) that corticosteroids may reduce retinal capillary permeability by increasing the activity and (or) density of the tight junctions in the retina capillary endothelium and (ii) that corticosteroids may inhibit the metabolic pathway of the vascular endothelial growth factor (VEGF), a major vascular permeability factor. Dexamethasone treatment also significantly reduced intracellular adhesion molecule-1 mRNA expression. In previous studies, leukocytes have been connected with VEGF production whereas leukocyte adhesion to the endothelium can cause disruption of tight junctions, thus increasing BRB breakdown and vascular permeability, eventually leading to edema. Also the steroids dexamethasone and triamcinolone acetonide affect unique sets of genes and appear to affect different pathways at different times and in different ways.

Pharmacokinetics And Safety

Graham and Peyman reported a 3-hour halflife of intravitreal-injected dexamethasone phosphate for the treatment of experimentally induced endophthalmitis in an animal model. Kwak and D’Amico performed further studies on the toxicity and pharmacokinetics of intravitreal dexamethasone and found a lack of retinal toxicity in doses of 440 μg of commercially prepared dexamethasone. They calculated the half-life of dexamethasone phosphate to be 3.48 hours in the rabbit model with no detectable levels after 72 hours. Beer et al were the first to report the pharmacokinetics of intravitreal TA (IVTA) in human eyes. They demonstrated that a single injection of 4 mg IVTA in a nonvitrectomized human eye maintained measurable concentration for up to 3 months. They also found that the half-life of TA in a patient who had undergone vitrectomy was shorter than 3.2 days. Chin et al found that the half-life of TA in vitrectomized rabbit eyes was 1.57 days and in the nonvitrectomized group was 2.89 days. Jonas investigated the aqueous concentration of TA after 25 mg IVTA injection in human eyes and found detectable levels of TA for up to 6 months postinjection. Detectable levels of TA have also been found for up to 8 months in silicone oil after IVTA injection of 25 mg. The safety of intravitreal corticosteroids was initially demonstrated in animal models. McCuen et al injected 1 mg of TA in 1 eye and saline in the other eye of 21 rabbits and found no significant retinal toxicity in drug-treated or control eyes during a 3-month follow-up period. Hida et al investigated the vehicles of a number of commercially available corticosteroids for possible toxicity when injected...
intravitreally. They found that the main vehicle for TA (benzyl alcohol) showed no retinal toxicity when used in standard or double concentration. Morrison et al.\(^2\) found that benzyl alcohol injected at concentrations modestly higher than that present in commercial TA (Kenalog, Bristol-Myers Squibb, Jacksonville, Fla.), was toxic to the rabbit eye. They also found histological changes in the outer retina, including loss and shortening of outer segments and Photoreceptors. In 2007, Lang et al.\(^2\) reported that, based on electrophysiological data, IVTA (4 mg/0.1 mL) does not cause functional toxicity to the outer retina of humans. In summary, it appears that intravitreal injection of TA in doses of 1 to 4 mg is nontoxic to the human retina. Higher doses of TA are also appearing to be well tolerated, with no evidence of retinal toxicity in humans. The current available evidence indicates that after 4 mg of IVTA, the medication can be present in the vitreous of a Nonvitrectomized eye for up to 3 months.

**Intravitreal Steroids For Diabetic Macular Edema**

According to the Early Treatment Diabetic Retinopathy Study (ETDRS), focal laser photocoagulation treatment of clinically significant DME substantially reduces the risk of visual loss\(^2\). However, in some patients, especially those with diffuse DME, this treatment may be ineffective. Despite laser photocoagulation, there are patients with refractory DME who continue to have visual loss. Recent prospective studies have shown that a single injection of 4 mg IVTA effectively reduces macular thickening due to DME and improves visual acuity (VA) in patients who have been unresponsive to laser treatment or in those who have had no previous treatment\(^2\).\(^2\),\(^2\),\(^2\).\(^2\),\(^2\).\(^2\),\(^2\). The reduction in the central macular thickness, as measured by optical coherence tomography (OCT), and improvement in vision may begin within the first 48 hours, reaches its maximal action in the first week, and lasts until around the third month of follow-up. At 6 months, it has been shown that up to 90% of patients may have recurrent macular thickening\(^2\). Various investigators\(^2\),\(^2\),\(^2\),\(^2\),\(^2\),\(^2\) have reported better effects with larger dose of IVTA (13–25 mg). The effectiveness of IVTA versus sub-Tenon injection of TA (SBTA) for the treatment of diffuse DME has been assessed by several investigators\(^2\),\(^2\),\(^2\),\(^2\). The Diabetic Retinopathy Clinical Research Network has investigated the use of intravitreal injection of triamcinolone acetonide (IVTA) for treatment of DME in two randomized clinical trials. One study\(^2\) compared two doses of IVTA, 1 mg and 4 mg, to focal/grid laser photocoagulation using a modified ETDRS protocol. The results showed that after 36 months there was a clear benefit for laser alone over IVTA. In the other study patients were randomly assigned to one of four groups: sham injection plus prompt laser, ranibizumab 0.5 mg plus prompt laser, ranibizumab 0.5 mg plus deferred laser, and IVTA 4 mg plus prompt laser. Though the steroid group did not show significant gain compared to the other groups, subgroup analysis, among individuals who were pseudophakic showed improvement in BCVA and reduction in macular thickness on OCT in the triamcinolone plus laser arm appeared comparable to the two ranibizumab arms through month 12. It has been suggested that the overall BCVA gains in the triamcinolone plus prompt laser group may have been masked by the development of cataract among the participants who were phakic.

**Intravitreal Steroids For BRVO**

The Branch Vein Occlusion Study (BVOS), a randomized, controlled clinical trial, set the standard for treating persistent ME caused by BRVO with focal grid laser photocoagulation\(^3\). However not all patients benefit from macular grid laser and this has led to several studies investigating IVTA as a possible alternative treatment\(^3\). Recently, a multicenter, randomized Phase III trial comparing the safety and efficacy of IVTA to treat vision loss associated with macular edema secondary to BRVO (SCORE-BRVO) comparing the efficacy and safety of IVTA for BRVO-associated macular edema with standard care (grid laser) showed no difference in vision between laser and the triamcinolone groups (1 mg or 4 mg) at 12 months\(^3\). Therefore the collaborators concluded that laser remains the benchmark of care. Also a highest rate of adverse events occurred in the 4-mg IVTA group.

**Intravitreal Steroids For CRVO**

The Central Vein Occlusion Study\(^4\) evaluated the efficacy of grid laser photocoagulation for ME secondary to CRVO and demonstrated that, although grid laser may lead to reduction of ME on fluorescein angiography, it has no beneficial effect on VA. Prospective reports\(^5\),\(^6\) of IVTA for ME secondary to CRVO showed that IVTA reduced ME and improved VA in 60% to 80% of patients with nonischemic CRVO with 6 months' follow-up. Treatment of ME in patients with ischemic CRVO resulted in anatomical improvement without visual improvement. Prospective case series reports\(^7\),\(^8\) showed significant improvement in VA after a single injection of IVTA that persisted for the first 6 months but was not sustained at 1 year. Recently, a multicenter, randomized Phase III trial comparing the safety and efficacy of IVTA to treat vision loss associated with macular edema secondary to CRVO (SCORE-CRVO) identified the superior efficacy of two doses of IVTA (1 mg and 4 mg) compared with observation. 34a The odds of achieving a >5 line improvement was five times greater with IVTA, with no difference between the 1-mg and 4-mg groups, although complications including elevated IOP and cataract were more common in the 4-mg group. From 12 months to two years, cataract formation may have attenuated the effect of IVTA on the mean change in visual acuity, yet the results still favored the two triamcinolone groups. Based on these results, treatment with 1 mg IVTA should be considered for patients with vision loss due to CRVO-related macular edema.
following a four-month retreatment interval.

**Intravitreal Steroids for Exudative ARMD**

Currently, there is insufficient evidence to support the use of IVTA as monotherapy for exudative AMD because most studies to date have not pointed to long-term efficacy. Recently, research has focused on a possible synergistic effect of verteporfin PDT and IVTA. The rationale behind combining the 2 treatments is that the inflammatory and exudative reaction following verteporfin therapy may be curtailed by the addition of a corticosteroid. In a small pilot study of combination treatment for subfoveal CNVM, Spaide et al found a mean VA improvement of 2.5 lines for newly treated lesions and decreased need for repeat therapy in all patients with 12 months of follow-up. A larger series of 184 patients demonstrated similar results, with a mean VA increase of 1.22 Snellen lines and a mean of 1.21 retreatments with an average 39-week follow-up. Chaudhary et al also showed, in a prospective randomized pilot study of PDT and IVTA (12 mg) versus PDT alone for occult and minimally classic subfoveal CNVMs, the need for fewer retreatments, reduction in the mean loss of VA, improved contrast sensitivity, and normalization of retinal thickness. Larger randomized studies are needed before combination therapy is used on a general basis.

**Intravitreal Steroids for Psuedophakic Cystoid Macular Edema**

Phacoemulsification with implantation of an intraocular lens can be complicated by postoperative CME. The current standard treatment includes topical steroids, topical nonsteroidal anti-inflammatory medications, and (or) oral acetazolamide and posterior sub-Tenon injection of repository steroids. However, some patients are resistant to the above-mentioned treatment. Current reports on the use of IVTA for pseudophakic CME appear to be small, uncontrolled pilot series. The amount of visual improvement is reported to be at least 2 Snellen lines, with maximum improvement up to 3.7 lines. One study found a persistent 15-letter gain in 5 of 6 patients with 6 months’ follow-up treated with a single injection of IVTA.

**Intravitreal Steroids for CME Secondary To Uveitis**

CME is known to be one of the most common vision threatening complications of uveitis. The incidence of CME is dependent on the underlying cause of uveitis. The mainstay treatment is corticosteroids given topically, periocularly, or systemically, and (or) second-line immunosuppressive agents. Despite these therapies, some patients remain refractory to treatment. As with studies on pseudophakic CME, studies recently published on the use of IVTA for the treatment of uveitic CME were retrospective, small, and uncontrolled. These studies have shown that a single injection of 4 mg IVTA can effectively reduce CME and improve VA in 50% to 70% of patients and allow the cessation of immunosuppressive therapy in some eyes. However, the period of effectiveness is variable (3–6 months). Factors associated with better response to IVTA include CME duration of less than 1 year, younger age, and no prior Vitrectomy.

**Intravitreal Steroid Sustained Release Devices**

For diseases like DME and macular edema due to vein occlusions that are chronic in nature, the lack of long-term efficacy of the traditional steroids combined with the adverse side effect profiles associated with high doses of steroids, has prompted the development of both biodegradable and nonbiodegradable intravitreal steroid delivery devices that release a smaller quantity of corticosteroid over a protracted period- Extended-release steroid delivery devices. The Ozurdex dexamethasone 0.7 mg intravitreal implant (Allergan, Inc.) received US Food and Drug Administration (FDA) approval in June 2009 for the treatment of macular edema following branch or central RVO. A phase 3 trial of the Ozurdex implant for the treatment of ocular inflammation in the setting of posterior and intermediate uveitis has just been reported. In addition, phase 3 trials of the implant are ongoing for the treatment of DME. The implant is biodegradable and is administered via a 22-gauge applicator; it delivers dexamethasone to the vitreous cavity via Allergan’s Novadur solid polymer delivery system. The Novadur system contains a poly D,L-sustained lactide-co-glycolide (PLGA) polymer matrix. In the GENEVA STUDY patients were randomly assigned to receive either a single treatment with the implant or sham injection. Vision improvement peaked at day 60, with 29.3% of patients in the implant group gaining three or more lines compared with 11.3% of patients in the sham group (P<.001) and maintained through day 90.

The other implants that have been trialled include Iluvien sustained-release fluocinolone acetonide device (Alimera Sciences), Verisome delivery system with triamcinolone acetonide (IBI-20089) (Icon Biosciences, Inc.), l-vation intravitreal triamcinolone acetonide implant (SurModics, Inc.), the Corticjet implant (NOVA63035, Novagali Pharma).

**Adverse Effects of Intravitreal Steroids**

Potential complications of intravitreal steroid treatment are divided into steroid-related and injection-related side effects. Steroid-related side effects include cataract formation and elevation in IOP. Injection-related side effects include retinal detachment, vitreous hemorrhage, bacterial endophthalmitis, and sterile endophthalmitis.

Thompson evaluated cataract progression in a retrospective study of 93 eyes treated with IVTA for ME. Posterior subcapsular cataract increased in 45.2% of eyes followed for at least 1 year. Gillies et al have analyzed cataract formation...
in eyes treated with IVTA for choroidal neovascularization. They found that nuclear sclerosis increased in 9.1% eyes, cortical cataracts in 12.1%, and posterior subcapsular cataracts in 24.2% of 33 eyes at 2 years. In the recent DRCR network DME study, almost 60% of eyes in the triamcinolone group underwent cataract surgery over 2 years of follow-up, compared with a 14% incidence of cataract surgery in the ranibizumab groups\textsuperscript{34a}. The incidence of cataract may be less with 1mg IVTA compared to 4mg IVTA. In the SCORE CRVO study the frequency of cataract was similar between the 1-mg IVTA and observation groups, conferring the 1-mg group a superior safety profile over the 4-mg group\textsuperscript{34a}.

Jonas et al reported on the effect of IVTA on IOP. In this meta-analysis involving 305 eyes 41.2% of patients developed IOP higher than 21 mm Hg, 11.4% higher than 30 mm Hg, 5.5% higher than 35 mm Hg, and 1.8% higher than 40 mm Hg. Steroid-induced IOP elevation was treated with antiglaucoma drops and 1% required filtering surgery\textsuperscript{26,43}. Mean IOP started to rise 1 week after injection and returned to baseline values approximately 8 to 9 months after injection. In the recent DRCR network study 28% of individuals in the triamcinolone group required intraocular pressure lowering medications during 2 years of follow-up, compared with roughly 4% in the ranibizumab groups and 5% in the laser. The incidence of elevated IOP may be less with 1mg IVTA compared to 4mg IVTA. In the SCORE CRVO study the frequency of glaucoma surgery was similar between the 1-mg IVTA and observation groups, conferring the 1-mg group a superior safety profile over the 4-mg group. 35 percent of the 4-mg group required IOP-lowering medication compared to only 20 percent of the 1-mg group\textsuperscript{34a}.

The risk of infectious (culture-positive) endophthalmitis after IVTA is low and studies have reported the incidence to be between 0.00% and 0.87%. The mean time of presentation has been 7.5 to 14 days postinjection. The presenting symptoms can be atypical with lack of pain, but severe vitritis and hypopyon are usually present. Risk factors include diabetes mellitus, filtering blebs, blepharitis, and multiuse triamcinolone bottles.\textsuperscript{54,55} The incidence of sterile (culture-negative) endophthalmitis has been reported to be between 0.1% and 1.6%. It usually presents earlier than infectious endophthalmitis, at 1.5 days after IVTA injection, and most cases recover baseline VA\textsuperscript{55}. There was no report of endophthalmitis in the IVTA group in both the DCR net DME study\textsuperscript{34} and the SCORE CRVO/BRVO study\textsuperscript{34,34a}. There were no cases of retinal detachment also in both these studies.

**Intravitreal Anti VEGF Therapy**

**Introduction**

The identification of one of the key mediators of angiogenesis happened in 1983 when Senger, Dvorak, and colleagues discovered a protein secreted from a guinea-pig tumor cell line that was a potent inducer of vascular leakage and named it vascular permeability factor (VPF). In 1989, Napoleone Ferrara and colleagues identified a molecule in the conditioned media from bovine pituitary follicular cells that promoted the proliferation of endothelial cells; they called it vascular endothelial growth factor (VEGF). Ultimately, the cloning of VPF by Daniel Connelly and others and VEGF by Ferrara’s group demonstrated that the 2 factors were the same protein.

**Role of VEGF**

The importance of VEGF as a therapeutic target derives from its roles in two of the most basic processes: neovascularization and vascular leakage. VEGF appears to be an important growth factor for angiogenesis and has been shown to be necessary in normal vascular development. VEGF is highly selective for vascular endothelial cells and induces angiogenesis by serving as a potent endothelial cell mitogen. It has been shown to be secreted by hypoxic RPE cells and induces endothelial cell proliferation and retinal vascular permeability. It has been identified as a major mediator of retinal ischemia-associated neovascularization. VEGF is up-regulated by hypoxia and its levels are increased in the vitreous and retina of patients and laboratory animals with active neovascularization from ischemic retinopathies such as proliferative diabetic retinopathy, central retinal vein occlusion and retinopathy of prematurity. Polarized secretion of VEGF by RPE cells is thought to direct VEGF toward the choroidal vasculature, where it may regulate choroidal integrity by binding to its receptors on the adjacent choriocapillaris.

VEGF over expression induces endothelial cell proliferation and increases vascular permeability, properties that can be detected clinically as the presence of fluid in the macula. Anti-VEGF therapy might reduce subretinal fluid, a theoretic possibility with VEGF inhibition\textsuperscript{57} resulting in short-term vision improvement.

The VEGF family includes placenta growth factor, VEGF-A, VEGF-B, VEGF-C, VEGF-D and VEGF-E. Briefly, VEGF-A plays a pivotal role in the development of pathologic angiogenesis in ischemic and inflammatory diseases. VEGF is a 35– to 45-kd homodimeric protein originally isolated as a vasopermeability factor and later cloned and identified as an angiogenesis factor. Up to six different VEGF isoforms are derived through alternative splicing of messenger RNA (mRNA). VEGF165 appears to be the isoform most responsible for pathologic ocular neovascularization. Hypoxia is a major regulator of VEGF expression which distinguishes VEGF from other growth factors that have been postulated to have a role in ocular neovascular diseases, including insulin-like growth factor-1, fibroblast growth factors (FGF), epidermal growth factor and placenta growth factor. Many cells in the eye produce...
VEGF and within the retina, these include RPE, pericytes, endothelial cells, glial cells, muller cells and ganglion cells. In the human eye, elevated vitreous and aqueous VEGF levels strongly correlate with retinal ischemia-associated neovascularization in conditions like diabetic retinopathy, retinal vein occlusion and retinopathy of prematurity.  

**Agents**

Anti-VEGF aptamers are stable small RNA-like molecules that bind exclusively and with high affinity to the 165-kDa isoform of human VEGF. Pegaptanib sodium, an oligonucleotide known as an aptamer, binds and inhibits only the extracellular isoforms of VEGF that are at least 165 amino acids in length. Multiple biologically active forms of VEGF-A are generated by both alternative mRNA splicing and posttranslational modification (proteolytic cleavage) and two of these forms (VEGF165 and VEGF121) have been detected in choroidal neovascular lesions. Pegaptanib sodium (MACUGEN, Pfizer) can only bind and inhibit the larger VEGF165 isoform. In contrast to pegaptanib, bevacizumab (AVASTIN; Genentech, South San Francisco) a full-length, humanized, murine full-length antibody with two binding sites for VEGF, ranibizumab is a humanized, murine antigen-binding fragment (Fab), bind and neutralize all the biologically active forms of VEGF (table 1). The similar VEGF binding properties of bevacizumab and ranibizumab can be explained by their common molecular lineage. Both drugs are proteins that were genetically modified from the same murine monoclonal antibody against VEGF. The two proteins differ in their size and affinity for VEGF (table 1). Whereas bevacizumab is a humanized, murine full-length antibody with two binding sites for VEGF, ranibizumab is a humanized, murine antigen-binding fragment (Fab) with only a single affinity-matured binding site for VEGF. Bevacizumab is currently approved as an intravenous treatment for metastatic colorectal cancer and its use in the eye is off-label.

**TABLE 1:** Pharmacokinetic differences between AVASTIN and LUCENTIS

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<th>AVASTIN</th>
<th>LUCENTIS</th>
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<tr>
<td>Size</td>
<td>149 KD</td>
<td>48 KD</td>
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<tr>
<td>Half life in serum</td>
<td>20 days</td>
<td>9 days</td>
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<td>Affinity to VEGF A receptor</td>
<td>less</td>
<td>high</td>
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<tr>
<td>Half life in vitreous</td>
<td>7-10 days</td>
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VEGF-Trap(AFLIBERCEPT, Regeneron pharma) is a fusion protein that combines ligand-binding elements taken from the extracellular domains of VEGFR-1 and VEGFR-2 fused to the Fc portion of IgG. This potent high-affinity VEGF blocker effectively suppresses tumor growth and vascularization in vivo, resulting in almost completely avascular tumors. Subcutaneous injections or a single intravitreal injection of VEGF-Trap(R1R2) strongly suppressed CNV in mice with laser-induced rupture of Bruch’s membrane, and subretinal neovascularization in transgenic mice expressing VEGF in photoreceptor cells. Trials involving intravitreal injections in exudative ARMD and retinal vein occlusion has been successful in humans.

RNAi (Sirna Therapeutics, Boulder, Colorado) is a double-stranded piece of interference RNA that is taken up by chorioretinal cells, activating a protein that breaks down the antisense mRNA. Destruction of VEGF mRNA prevents the production of VEGF protein. The whole process is catalytic, so the RNAi may be a very potent and efficient blockade of VEGF. RNAi may have a long biologic half-life, indicating a much longer interval between intravitreal injections. Anti-VEGF RNAi for the treatment of CNV is currently being tested in clinical trials.

**Anti VEGF Therapy In Exudative ARMD**

The first study with pegaptanib sodium – MACUGEN was the multicenter VEGF Inhibition Study in Ocular Neovascularization (VISION trial) which enrolled 1190 patients. They were treated with either 0.3 mg, 1.0 mg, or 3.0 mg of pegaptanib every six weeks (n = 892), or with a sham injection. The study included all lesion subtypes: predominantly classic, minimally classic, and occult with no classic CNV. At 54 weeks follow-up, patients treated with pegaptanib showed significantly better clinical benefit compared with patients in the placebo group. Overall, 70% of patients treated with pegaptanib sodium experienced a vision loss of less than 15 ETDRS letters, compared with 55% of patients who received a sham injection. No difference in outcomes was detected among patients who received either 1.0 mg or 3.0 mg and the treatment effect was consistent regardless of baseline visual acuity, lesion sub-type or size of lesion.

Published studies involving patients treated with 1.25 mg intravitreal bevacizumab- AVASTIN injections spaced one month apart, have demonstrated significant improvements in retinal thickness in as little as one week after the first injection, and significantly better improvements in VA. Such improvements appear to be sustained over several months. No significant adverse events or other safety issues have been identified in any of the studies with bevacizumab.

The first study with ranibizumab (Minimally Classic/Occult Trial Age-Related Macular Degeneration, or MARINA) was a two-year, phase III trial designed to evaluate monthly injections in 716 patients with minimally classic or occult with no classic lesions. They were randomized 1:1:1 to receive either sham injections (n = 238), or injections of ranibizumab at 0.3 mg (n = 238) or 0.5 mg (n = 240). The
12-month primary endpoint analysis revealed that at least 94% of patients in both arms receiving ranibizumab lost fewer than 15 letters, compared with 62% of patients in the sham treatment arm. A gain in VA of at least 15 letters was observed in 25% of patients in the 0.3 mg ranibizumab arm, and 34% of patients in the 0.5 mg ranibizumab arm. The gains in visual acuity occurred regardless of lesion type or size, or baseline VA, and were evident within seven days of the first injection. The ANCHOR study (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration) compared the same two dosage strengths of ranibizumab against PDT in 423 patients who were followed out to 12 months. At that point, patients in the ranibizumab 0.5 mg arm gained, on average, 11.3 letters, while patients in the PDT arm lost, on average, 9.5 letters, for an overall difference in treatment effect of 20.8 ETDRS letters. The outcomes were more or less similar at month 24. In addition, approximately 95% of patients in both ranibizumab arms lost fewer than 15 letters, while 35% and 40% of patients in the 0.3 mg and 0.5 mg arms respectively gained more than 15 letters compared with patients who were treated with PDT. Interestingly, a sub-group analysis reported that as lesion size increased, the benefit of ranibizumab 0.5 mg became less significant when compared with PDT.

Because VEGF inhibitors have a short half-life, their effects wear off fairly quickly. Regular injections of ranibizumab could therefore be needed indefinitely. In the two main ranibizumab trials cited here most of the benefit occurred within the first three months of treatment. The improvements in VA between months 3 and 12 were modest at 1.8 and 1.5 letters for the two studies, respectively. Therefore, it was reasoned that patients might be able to achieve significant gains in VA within the first three months, and that additional treatments could be given on an "only as needed" basis. In the Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with intra-Ocular ranibizumab (PrONTO) trial68 patients received ranibizumab 0.5 mg at baseline, and then again at months 1 and 2. They did not receive additional treatments unless certain pre-specified criteria were met. These criteria included a loss of more than 5 ETDRS letters, and/or an increase in macular thickness of at least 100 microns, continued subretinal fluid detected by optical coherence tomography (OCT) after one month, new hemorrhage, and new neovascularization. An analysis of 37 patients produced encouraging data in terms of reduced retinal thickening, and improved VA.

In a second study, (A Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration; PIER)69 patients received injections of ranibizumab 0.3 mg or 0.5 mg, or a sham, at baseline, and then again at months 1 and 2. Further injections were given at three-month intervals (ie, months 5, 8, 11), for a total of six injections over 11 months. Initially, patients receiving the higher dose of 0.5 mg ranibizumab had a 4.3 letter gain in VA over the first three months (ie, while monthly injections were being given), but this gain quickly deteriorated once quarterly dosing was commenced. At the end of 12 months, these patients had a mean decrease in VA of 0.2 letters from baseline. Currently based on these experiences it is recommended that OCT findings should be considered for the adjustment of the dosing regimen and PRN regime is an effective strategy.

The National Eye Institute instituted CATT trial to compare Lucentis and Avastin for treatment of wet AMD70. Patients were randomly assigned and treated with one of four regimens for a year. They received Lucentis monthly or PRN, or Avastin monthly or PRN. In the monthly treatment arms, Avastin was equivalent to Lucentis, with 8.0 and 8.5 visual acuity letters gained, respectively, and in the as-needed arms, Avastin was equivalent to Lucentis with 5.9 and 6.8 letters gained. In addition, no difference was found in the percentage of patients who had an important gain or loss in visual function. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 μm) than in the other groups (152 to 168 μm, P=0.03 by analysis of variance). However each drug when given on a PRN schedule, there also was no difference (within one letter) between drugs. PRN dosing required four to five fewer injections per year than monthly treatment. Visual gains were about two letters less with PRN than with monthly treatment but overall visual results were still excellent.

**AntiVEGF Therapy in DME**

Pegaptanib sodium (MACUGEN) was studied in a phase II trial for DME71. In that study, 172 subjects with DME were randomized to receive a series of 3 intravitreal injections of pegaptanib (at entry and every 6 weeks) in 1 of 3 doses, or a sham injection, and were followed for 36 weeks. Additional injections or photocoagulation were permitted every 6 weeks through the end of the study. At the 36-week mark, mean visual acuity had improved to 20/50 in the pegaptanib 0.3-mg group (the dose that was approved by the FDA) versus only 20/63 in the sham group (P = 0.04). Mean central retinal thickness decreased by 68 mcmin the 0.3-mg group, whereas it increased by 4 mcmin the sham group (P = 0.02). In addition, photocoagulation was required in 25% of the 0.3-mg group compared with 48% of the sham group (P = 0.04). The injections were well tolerated, with a single case of endophthalmitis reported (1/652 injections, 0.15%).
Various studies have reported the benefit of intravitreal bevacizumab in diabetic macular edema. A recently published systematic review and meta-analysis to evaluate the effect of bevacizumab (Avastin) in diabetic macular edema assessed change in central subfield macular thickness (CSMT) in μm and best-corrected visual acuity (BCVA) in log MAR equivalents were extracted at 6, 12 and 24 weeks, and results compared between groups receiving intravitreal bevacizumab (IVB), a combination of IVB and intravitreal triamcinolone acetonide (IVT), and macular laser photocoagulation or sham control groups. The summary mean difference indicated a statistically significant reduction in CSMT at 6 weeks when treated with bevacizumab compared to control. IVB treatment, however, lost significance at 12 weeks and 24 weeks. The summary mean difference in BCVA for IVB group compared to control reached significance only at 6 and 24 weeks. Combination therapy of IVB and IVT did not result in any significant reduction in CSMT or gain in vision compared to treatment with IVB alone at any point in time.

More recently, the DRCR.net conducted a randomized controlled trial to assess whether ranibizumab (Lucentis), combined with either prompt or deferred laser, or intravitreal triamcinolone acetonide combined with prompt laser, might result in improved visual acuity outcomes in comparison with the gold standard of focal/grid photocoagulation for DME. Throughout the first year, the median number was eight in the ranibizumab plus prompt laser group and nine in the ranibizumab plus deferred laser group. In the second year, the median number of injections in those groups was again two and three, respectively. In the ranibizumab plus deferred laser group, laser could not be considered until week 24, and then only if edema persisted and the eye was no longer improving with each injection. With those criteria, approximately 28% of eyes in this group underwent laser treatment in year 1. During year 2, an additional 14% received laser. Therefore, through 24 months in the ranibizumab plus deferred laser group, nearly 60% of eyes never received laser. All patients in the ranibizumab plus prompt laser group underwent initial laser treatment following their first study injection of ranibizumab.

In year 1, approximately 70% of eyes in this group received at least one additional laser. In year 2, nearly half in this group received laser again. The mean improvements in BCVA letter score from baseline to month 24 were: -10.2 letters and 24 months in the ranibizumab plus prompt laser group, -7.1 letters in the ranibizumab plus deferred laser group, and -3.5 letters in the triamcinolone plus prompt laser group. A greater percentage of eyes in the ranibizumab groups achieved a substantial improvement in BCVA of two or more lines (10 or more letters) at 1 year: Fifty percent in the deferred laser group and 47% in the prompt laser group, compared with 30% in the laser alone group. Gains of three lines or more at 1 year were also more common in the ranibizumab groups than the other groups. The anatomic findings on OCT confirmed the visual acuity results; the ranibizumab groups had the most rapid decreases in thickness and relatively flat curves through 2 years. At 2 years there was still a significant difference of about 30 μm between the ranibizumab groups and laser alone.

**Anti VEGF Therapy in Retinal Vein Occlusion**

A phase II randomized, double-masked, multicentre trial evaluated the role of pegaptanib in CRVO patients and showed that eyes receiving Macugen gained a mean of 10 ETDRS letters compared with a mean loss of two letters in the eyes receiving sham injections. Treatment of CRVO and BRVO with intravitreal bevacizumab achieved significant reductions in vein diameter, tortuosity, optic disc oedema and macular thickening, with some gain in vision as reported by various authors both as primary therapy and in nonnaive eyes. Most of the effect were short term and patients required repeat injections to maintain visual benefits obtained.

The BRAVO trial, a phase 3 multicenter clinical study of BRVO, showed that patients receiving 6 monthly injections of 0.3 mg or 0.5 mg ranibizumab experienced a mean improvement of 16.6 and 18.3 letters, respectively, in visual acuity, compared with 7.3 letters improvement in those receiving sham injections. The percentage of patients who gained three lines (15 letters) of visual acuity was 55.2% and 61.1% in the 0.3 mg and 0.5 mg ranibizumab groups, respectively, compared with 28.8% of patients receiving sham injection. That improvement was maintained during the PRN phase, and again the patients in the sham injection group also improved once they had access to ranibizumab treatment, although not to the same levels as the treatment groups. There were rapid reductions in excess foveal thickness with ranibizumab treatment, and by months there was a substantial mean difference from baseline.

The CRUISE study involved patients with CRVO receiving six monthly injections of ranibizumab had substantial improvement in visual acuity: 12.7 letters with 0.3 mg and 14.9 letters with 0.5 mg ranibizumab injections, in comparison with 0.8 letters in sham-treated patients. Once those in the sham group were able to receive ranibizumab they also improved, but did not achieve the level of improvement seen in patients treated in the first 6 months of the study. Similar results were seen regarding the percentage of patients who gained at least 3 lines of VA: 46.2% with 0.3 mg and 47.7% with 0.5 mg ranibizumab, compared with 16.9% of sham-treated patients. In the 2-year follow-up of patients with CRVO after the initial three monthly injections, these patients experienced a mean gain of 12 letters at 3 months, but by month 24 the mean gain had decreased to 8.5 letters.
Anti VEGF Therapy in Other Conditions

Anti VEGF Therapy in Glaucoma

Part of the concern over IOP elevation after anti-VEGF injection is due to the increasing popularity of using these agents in various ophthalmic indications. However, whereas multiple intravitreal injections of anti-VEGF agents may well be a cause of IOP elevation, anti-VEGFs have also proven invaluable in the reduction of IOP, especially due to glaucoma subtypes involving neovascularization. Historically, neovascular glaucoma is treated with a combination of medication to lower IOP and laser panretinal photocoagulation to abate angiogenesis. Several studies have reported rapid regression of NVI following intravitreal injection of bevacizumab®. The combination of PRP and IVB seems an appropriate treatment for NVG; IVB prevents angle closure in the time PRP needs time to take effect. Systematic review of the efficacy and safety of intravitreal bevacizumab (IVB) in the treatment of neovascular glaucoma (NVG) establishes bevacizumab is well tolerated, effectively stabilizes NVI activity, and controls IOP in patients with NVG when used alone and at an early-stage of NVG. Anti-VEGF therapy may find its way into other areas of glaucoma management as well. Various authors are involved in research exploring the use of ranibizumab at the time of trabeculectomy surgery to modulate the wound healing process. What has been found in early experimental studies is that the addition of an injection of anti-VEGF to the use of mitomycin C results in a healthier-looking bleb postoperatively. Although there was equal pressure-lowering efficacy in patients treated with MMC alone and patients treated with MMC and ranibizumab, the latter group of patients had blebs that appeared to be less elevated and more diffuse with less vascularity.

Retinopathy of Prematurity (ROP)

ROP is characterized by incomplete vascularization of the peripheral retina in a premature neonate leading to retinal neovascularization. Risk factors for ROP include premature birth, low birth weight and oxygen therapy. The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Study demonstrated that ablation of the peripheral avascular retina reduced the risk of poor structural and visual outcome due to retinal distortion or detachment in ROP (1980's). The ablated retina is not functional and is not amenable to regeneration. Peripheral retinal ablation is not universally effective in fostering regression of ROP. This is particularly true for an aggressive form of ROP (aggressive posterior ROP, or APROP) which typically affects profoundly premature and infirm neonates. In this subset of infants, progression of ROP to bilateral retinal detachment and blindness occurs despite timely and complete peripheral retinal laser ablation. Increased levels of VEGF in the vitreous have been reported in patients with ROP. BEAT-ROP (Bevacizumab eliminates the angiogenic threat of retinopathy of prematurity) study is a prospective, controlled, randomized, stratified, multicenter trial to assess intravitreal bevacizumab monotherapy for zone 1 or zone II posterior stage 3+ (i.e., stage 3 with plus disease) retinopathy of prematurity. Infants were randomly assigned to receive intravitreal bevacizumab (0.625 mg in 0.025 ml of solution) or conventional laser therapy, bilaterally. Intravitreal bevacizumab monotherapy, as compared with conventional laser therapy, in infants with stage 3+ retinopathy of prematurity showed a significant benefit for zone I but not zone II disease. Development of peripheral retinal vessels continued after treatment with intravitreal bevacizumab, but conventional laser therapy led to permanent destruction of the peripheral retina. There are numerous safety concerns, and it is one of the most difficult aspects of considering anti-VEGF therapy in neonates. VEGF is an important growth factor in normal vascular development in infants; might blockade of VEGF activity be detrimental and tip the risk-benefit ratio in ROP therapy? Additionally, infants with ROP typically have significant comorbidities, and the interaction of anti-VEGF therapy with other health problems is unknown. It is also not known at what rate injections should be given or what kind of injection-related complications, such as infection or retinal detachment, may occur.

Other Applications of Anti VEGF Therapy

CNV may be seen in conditions other than AMD such as high myopia, angiod streaks, ocular histoplasmosis, idiopathic juxtafoveal telangiectasia, secondary CNVM and choroidal osteoma. Anti-VEGF therapy in these conditions is almost limited to off-label use of bevacizumab and there are a few small-sized reports in the literature in this regard. In eyes with proliferative diabetic retinopathy intravitreal bevacizumab is helpful in resolution of vitreous hemorrhage, regression of NVI, reduces bleeding during vitrectomy when injected preoperatively and management of recurrent postvitrectomy bleed and anterior hyaloid proliferation. Anti VEGF therapy has also been reported to be useful in management of persistent macular edema postcataract surgery, uveitis, coats disease and other pathologies. The use of Anti VEGF therapy as an adjuvant therapy in ocular tumors is also being explored.

Safety Issues With AntiVEGF Therapy

In general, few serious adverse events have been reported following ocular treatment with anti-VEGF drugs. In the MARINA and ANCHOR trials of the most frequent ocular adverse events included local injection site and ocular inflammation, as well as spikes in intraocular pressure, which could be significant but appeared to be transient. A metaanalysis on ranibizumab published revealed that
serious adverse ocular events, occurred in < 0.1% of intravitreal injections in the various trials and included retinal detachment and endophthalmitis. Less serious adverse ocular reactions occurring in < 2% of patients included intraocular inflammation and increased intraocular pressure. In patients who received bevacizumab ocular adverse events were seen in 3% of patients. Case reports of RPE tears following anti-VEGF administration have been reported. There is a wide variance in the incidence of these tears, ranging from less than 1 to 17%. and can result in significant, permanent loss of vision. Most cases of RPE tear occur in the presence of pigment epithelial detachment (PED) lesions, and it appears that foveal vascular lesions are more susceptible to RPE tears than serous lesions. It is reported that the risk of developing an RPE tear correlates directly with the diameter of the PED size, as well as with the presence of subretinal fluid as seen on OCT.

In the VISION trials, serious systemic events, such as stroke, hypertension, and hemorrhagic complications, occurred at the same rate as placebo. In the MARINA and ANCHOR trials, serious nonocular adverse events were similar in the ranibizumab groups compared with controls. Adverse events that did occur more frequent in patients receiving the higher 0.5 mg dose. Arteriothrombolic events, which include nonfatal myocardial infarction and/or stroke, and death from other vascular causes, were seen in 3.8% of patients receiving 0.3 mg of ranibizumab and 4.6% of those receiving the 0.5 mg dose. Longer follow up from the SAILOR study have clarified these findings. Results from the recently published CATT trials have revealed that Rates of death, myocardial infarction, and stroke were similar for patients receiving either Lucentis or Avastin. The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with Avastin than with Lucentis (24.1% vs. 19.0%; risk ratio, 1.29), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern.

Conclusion

The introduction of intravitreal pharmacological agents like steroids and anti-VEGF molecules have revolutionized the management of neovascular ARMD, macular edema of retinal vascular diseases like diabetic retinopathy and vein occlusions. Its role in the management of other causes of macular edema and retinal neovascularisation, is still investigational though anecdotal case reports have established its effectiveness. Anti-VEGF therapy is the current gold standard in the management of neovascular ARMD and the role of intravitreal steroids is debatable. Along with laser treatment anti-VEGF therapy or steroids have become the mainstay in the management of macular edema in patients with diabetic retinopathy and vein occlusion. These agents in isolation or as part of combination therapy have established to be effective in various other retinal and choroidal pathologies and the indications for their use is ever increasing. The risk of ocular side effects have to be kept in mind when these agents are used and discussed with the patient. Complications such as increased IOP, and cataract progression must be expected during intravitreal steroid therapy. Systemic complications are a concern during anti-VEGF therapy. The cost of therapy should also be kept in mind when planning these treatments as most of the diseases where it is used are chronic and needs repeat injections. The frequency of treatment and the duration of treatment with these agents will continue to be investigated and the future will probably will give us more answers.

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