The Injectables: What, When, and Which One?

Updates on Intravitreal Anti-VEGF drugs and steroids

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Vascular endothelial growth factor (VEGF) and inflammation. VEGF-A circulates normally in the body and is essential in endothelial cell growth. In the pathological state in the eye, hypoxia increases VEGF-A, promotes growth of neovascularization and accelerates the breakdown of blood-retinal barrier and build-up of fluid in or under the neurosensory retina and retinal pigment epithelium (RPE). It has 6 isoforms; the predominant isoform (most common of which) is VEGF 165 and is most linked to neovascularization in the eye. VEGF-A provided the rationale for targeted drug development. Anti-VEGF drugs are anti-angiogenic, anti-inflammatory, anti-fibrotic, and anti-permeable. The rationale for the use of steroids to treat macular edema is related to their ability to reduce capillary permeability, to inhibit the expression of VEGF gene, and to inhibit the metabolic pathway of VEGF.[1,2]

Anti-VEGF drugs. Currently used anti-VEGF drugs include ranibizumab (Lucentis), aflibercept (Eylea), and bevacizumab (Avastin); all of which bind to VEGF-A. Ranibizumab is a 48 kDa Fab-only antibody fragment while bevacizumab is a larger 149-kDa full-length antibody. Afliberpcept is a 115 kDa soluble decoy receptor fusion protein attached to the Fc component of human IgG (ICG). The relative molar binding activities of ranibizumab, aflibercept, and bevacizumab are 1, 140 and 0.2 respectively, indicating a lower binding affinity for bevacizumab. The binding affinity of aflibercept is higher than ranibizumab and bevacizumab because of its 2 receptors for VEGF. The intravitreal half-lives of ranibizumab, aflibercept, and bevacizumab are estimated to be 3, 5, and 7 days respectively. The systemic half-lives of ranibizumab, aflibercept, and bevacizumab are computed to be 2 hours, 5-6 days, and 20 days respectively. The systemic retention of aflibercept and bevacizumab maybe prolonged because these contain an Fc portion that binds to an endothelial cell receptor and is recycled systemically.[3-7]

Both ranibizumab (0.5 mg/0.05 mL) and aflibercept (2 mg/0.05 mL) are FDA-approved for monthly intravitreal injection for neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), macular edema following retinal vein occlusion (RVO), and pathologic myopia. For ranibizumab, it is recommended that patients with nAMD be treated with 3 monthly loading doses of ranibizumab followed by monthly dosing.[5] On the other hand, aflibercept is dosed less frequently at every 2 months after 3 monthly loading doses for nAMD.[6] Both ranibizumab and aflibercept are FDA-approved for monthly dosing for DME and macular edema following RVO.[5,6] Bevacizumab is FDA-approved for intravenous use in the treatment of metastatic colorectal and non-small cell lung cancer. Because bevacizumab and VEGF have similar binding patterns, it is hypothesized that bevacizumab may be as effective as ranibizumab in the treatment of intraocular neovascularization. It was investigated first as a systemic intravenous treatment for nAMD and then as an intravitreal injection.[7] Since 2005, multiple uncontrolled and retrospective case series have indicated that monthly intravitreal bevacizumab has a beneficial effect in the treatment of nAMD, DME, and macular edema following RVO. Bevacizumab is split from the original vial into single doses (1.25 mg/0.05 mL) by a compounding pharmacy or by the attending ophthalmologist.

Intravitreal steroids. Intravitreal triamcinolone has been proven to be effective in RVO and similarly in DME.[8,9] First generation steroid implants, such as 0.59 mg fluocinolone (Retisert), also showed promise. However, the high rate of cataract formation and steroid-induced glaucoma of triamcinolone and earlier fluocinolone implants outweighed the visual gains.[8,9,10] To provide a sustained delivery of corticosteroid with fewer side effects, a dexamethasone implant (Ozurdex) was developed. It is in a prefilled, single-use applicator containing 0.7 mg of dexamethasone in a slow-release polyglycolate-acetate biodegradable implant providing dexamethasone up to 6 months in the posterior cavity. It is FDA-approved for pseudophakics or phakics who are scheduled soon for cataract surgery with DME, macular edema for RVO, and posterior uveitis. It is recommended that said patients receive Ozurdex injection once every 6 months.[11]

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EFFICACY

Neovascular AMD. Intravitreal anti-VEGF therapy is the most effective way to manage nAMD and represents the first line of treatment.[12,13] Other therapies, such as verteporfin photodynamic therapy (PDT) and laser photocoagulation, are seldom needed for newly diagnosed nAMD with subfoveal and juxtafoveal choroidal neovascularization (CNV), but may be used in combination with anti-VEGF agents or as an alternative in unresponsive cases. Laser treatment in CNV is guided by the MPS study.[14]

Ranibizumab is effective for all subtypes of nAMD, based on the MARINA and ANCHOR studies.[15,16] Aflibercept has been reported to be non-inferior and clinically equivalent in efficacy to ranibizumab according to the VIEW trials.[17] Comparative trials and uncontrolled case series, such as the PACORES and ABC trials, reported improvements in visual acuity and decreased retinal thickness with bevacizumab.[18,19] The CATT study was a multi-center trial that compared the safety and effectiveness of bevacizumab to ranibizumab and an individualized dosing regimen (as needed or PRN) to monthly injections. In 2 years, the CATT study found that bevacizumab is non-inferior to ranibizumab[20]. Similar results were seen in the 2-year IVAN trial conducted in the UK.[21] Both CATT and IVAN concluded that there did not appear to be a significant difference in the efficacy between ranibizumab and bevacizumab.[20,21] At present, there is no role for anti-VEGF drugs in geographic atrophy secondary to nAMD. All 3 anti-VEGFs currently demonstrated comparable efficacy for nAMD and either may be used as first-line treatment.[3,12]

Diabetic Macular Edema. Intravitreal anti-VEGF drugs are the initial treatment of choice for center-involving DME, with possible subsequent or deferred focal laser treatment.[22] When center-involving DME is present, the anti-VEGF therapies provide a better VA and anatomic outcome than focal/grid laser surgery alone. At this time, laser photocoagulation is the preferred treatment for non-center involving DME and is guided by the ETDRS study.[22,23]

Ranibizumab is more effective than focal/grid laser for center-involving DME according to the READ-2 study.[24] Further phase III trials, such as RESTORE, RESOLVE, RISE and RIDE studies, conclusively established the beneficial effects of ranibizumab versus laser.[25,26,27] DRCR.net Protocol I study also showed that ranibizumab, with either prompt or deferred laser, was better than either laser alone or laser combined with intravitreal triamcinolone.[28] The BOLT study is a 24-month RCT that showed favorable outcomes for bevacizumab over laser in eyes with center-involving DME.[29] Similarly, the DA VINCI study demonstrated better outcomes of aflibercept over laser.[30] Two-year results of the ongoing VISTA and VIVID studies have reported that both monthly and every 2 months aflibercept reduced severity of DME in more patients than laser.[31] The DRCR.net Protocol T trial is a head-to-head direct comparison study of all 3 anti-VEGF drugs for center-involving DME and concluded that all 3 have comparable efficacy.[32] Currently, all 3 anti-VEGFs may be used as first-line treatment.[22,32]

The MEAD study evaluated the efficacy of dexamethasone implant (Ozurdex) in DME and demonstrated at least 15-letter improvement in BCVA from baseline in 22.2% patients receiving the 0.7 mg implant.[33] Currently, all 3 anti-VEGF drugs and intravitreal dexamethasone implant (Ozurdex) provide the most favorable visual outcomes, over laser and triamcinolone, in the treatment of center-involving DME.[22,32,35]

Macular Edema following Retinal Vein Occlusion. Treatment of center-involving macular edema secondary to retinal vascular occlusions currently includes intravitreal anti-VEGF drugs and intravitreal steroid implants. Laser photocoagulation may still be considered in non-center involving macular edema secondary to BRVO.[36]

According to the CRUISE and BRAVO studies, ranibizumab is effective in CRVO and BRVO, respectively.[37] GALILEO and COPERNICUS studies supported the efficacy of aflibercept in the treatment of CRVO.[38,39] When compared to focal/grid laser, the VIBRANT study reported that monthly aflibercept had more visual gains compared to lasered eyes with BRVO.[40] Although there is no RCT involving bevacizumab in RVO, many uncontrolled case series have reported that it can lead to VA improvement and resolution of macular edema. However, because of the variation in dosing and treatment regimens among these studies, both long-term outcomes and safety data remain unclear.[41]

The SCORE study showed the efficacy of intravitreal triamcinolone for BRVO and CRVO. However, when compared to laser treatment, it had more negative side effects.[8] The GENEVA study

demonstrated the efficacy of dexamethasone implant (Ozurdex) with BRVO and CRVO.[42] Currently, intravitreal anti-VEGF therapies and Ozurdex are preferred over laser for the treatment of macular edema secondary to BRVO and CRVO.[36]

Treatment pearls. Changes in anatomy may precede the clinical changes in physiological manifestations, such as visual acuity. This lack of correlation between visual acuity and central retinal thickness has influenced the design of newer clinical trials.[35] With much improved structural and functional outcomes with anti-VEGF therapy, criteria for treatment have changed to include patients with even better BCVA at baseline --- early intervention. Benefits of early intervention with anti-VEGF drugs have been shown in the treatment of nAMD, DME, and macular edema following RVO.[35,43,44] The GENEVA study also supported that early treatment with Ozurdex dexamethasone implant was shown to be more beneficial than delayed treatment in restoring VA.[42]

Improvements in VA after treatment with anti-VEGF for nAMD, DME, and macular edema from RVO were documented as early as 3 months, 1 month, and 7 days respectively.[13,28,37] The GENEVA study reported visual improvements with Ozurdex as early as 7 days with a peak of 2 months.[42] The greatest variability in outcomes with anti-VEGF appeared to be highest in the patient groups who had the worst baseline VA.

Late responders with anti-VEGF in nAMD, DME, and macular edema from RVO were associated with less frequent injections and less frequent monitoring. Late responders with nAMD were observed to have diffuse RPE abnormalities, occult lesions, and advanced age.[12] It was recommended that non-responders be switched to a higher dose, switched to another anti-VEGF agent, or add a combination treatment (i.e. combination with focal laser for DME).[45,46]

The 2 accepted treatment schemes that deviate from the FDA-approved monthly dosing include: (1) treat-and-extend, and (2) treat-and-observe or PRN. Treat-and-extend scheme pertains to treatment that is continued at gradually increasing intervals based on treatment response. Once the lesion and VA have stabilized on the monthly therapy, the time to the next scheduled exam or treatment is extended by 2 weeks to a maximum of 12 weeks. PRN treatment scheme pertains to retreatment that is only performed for signs of recurrent exudation seen in OCT. OCT is more sensitive than VA in detecting exudation in the retina. Both treatment schemes have been shown to be effective in nAMD and DME.[12, 46-48] Monthly loading doses of anti-VEGF drugs are no longer recommended for DME and macular edema following RVO.[49]

For patients who prefer treatment options apart from monthly dosing of anti-VEGF, PRN and treat and extend treatment schemes are effective options.[17,20,21] Steroids provide a viable alternative to anti-VEGF agents for non-responders or those who prefer the mode of delivery of every 6 months steroid over monthly or every 2 months anti-VEGF injections.[34]

SAFETY

Ocular safety. Intravitreal injections are generally well-tolerated and rarely associated with serious adverse events, such as endophthalmitis. Intraocular use of bevacizumab has incidentally been associated with non-infectious and infectious endophthalmitis and is associated with inappropriate compounding and dispensing.[3] Sterile preparation of single doses of bevacizumab is recommended with timely usage to prevent contamination spreading and formation of aggregates. Other complications included macular ischemia, retinal hemorrhage, and retinal detachment. Anti-VEGF agents have been reported to contract existing fibrovascular tissue, cause retinal tears and precipitate traction retinal detachment.[22] GENEVA and MEAD studies reported low cataract rate and low rates of IOP increase with dexamethasone implant (Ozurdex). It was noted that moderately raised IOP peaked at month 2, was controlled medically, and declined in 4-5 months.[33,42]

Systemic safety. Systemic safety issues with anti-VEGFs included arterial thromboembolic events, cerebrovascular events, and gastrointestinal events such as gastrointestinal bleeding. The DRCR.net Protocol T trial reported that ranibizumab, aflibercept, and bevacizumab have comparable cardiovascular safety profiles.[32] Bevacizumab is used systemically in cancer treatment and it is in that setting that it is associated with an increased risk of cardiovascular events and cerebrovascular accidents.[52] However, much smaller doses are used intravitreally and most studies have not demonstrated increased

cardiovascular risk when compared to ranibizumab. This observation was also described in the CATT and IVAN trials comparing ranibizumab and bevacizumab.[20,21] However, randomized controlled trials powered to study safety are still underway and will conclusively establish the issue in safety.

CONCLUSION

All currently available anti-VEGF drugs and dexamethasone implants are effective in their respective treatment indications. RCTs powered to prove safety are still underway but safety sub-analysis of randomized controlled trials on efficacy show good tolerability. Ideally, we should maximize the benefits and reduce the burden of cost and exposure to treatment-related adverse effects. Factors affecting drug selection include patient characteristics and patient and physical preferences. Patient characteristics include lens status, pre-existing glaucoma, pregnancy, cardiovascular status, and whether patient is treatment naïve or treatment resistant. Patient and physician preferences include patient compliance, frequency of dosing, availability, cost, and physician familiarity. Striking a balance between efficacy, safety, and feasibility is important for maximizing visual outcomes and achieving optimal patient care.

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