Emerging Treatments

for Diabetic Macular Edema

A review of agents in clinical trials.

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One of the most prominent and debilitating microvascular complications of diabetes is diabetic retinopathy, the most common cause of blindness among adults of working age in the United States,[1] responsible for 12,000 to 24,000 new cases of blindness each year.[2] The primary source of mild to moderate vision loss associated with diabetic retinopathy is diabetic macular edema (DME), an abnormal collection of extracellular fluid in the macula due to a breakdown of the blood-retinal barrier.[3]

While focal/grid laser photocoagulation, the standard of care for the past 25 years and the only currently US Food and Drug Administration (FDA) approved treatment for DME, has consistently shown efficacy in clinical trials, laser treatment is not without potential complications, and new treatments are necessary for those who are either unresponsive to laser photocoagulation or show a less than ideal response. To fulfill this unmet need, several pharmaceutical therapies for DME are currently in clinical development, the majority of which are intravitreally injected antiinflammatory or antiangiogenic agents. These include vascular endothelial growth factor (VEGF) inhibitors such as ranibizumab (Lucentis, Genentech), VEGF trap (VEGF Trap-Eye, Regeneron) and pegaptanib sodium (Macugen, OSI Eyetech, Inc.), and intravitreal delivery systems, which release corticosteroids such as fluocinolone acetonide (Iluvien, Alimera), dexamethasone (Ozurdex, Allergan, Inc.), and triamcinolone acetonide (I-vation SurModics, Inc.).

ADVANCEMENTS IN STEROID THERAPY

Increased production of inflammatory mediators and vascular permeability factors as well as the loss of endothelial tight junction proteins are found in patients with DME, and all these processes are known to be modulated by corticosteroids. Even prior to the recent emergence of randomized, controlled clinical trials evaluating their safety and efficacy for DME, steroids (especially triamcinolone acetonide) have been used off-label by practitioners relying on case studies and series and results of their use for other retinal diseases.

The primary means of steroid delivery for macular edema has been intravitreal injections, which bypass the blood-retinal barrier and provide a higher concentration of dose at the target site for a longer period of time compared with Sub-Tenon's or peribulbar injections.[4] These injections, however, are often associated with both steroid-related adverse events, including cataract formation and elevated IOP, and less common injection-related side effects such as retinal detachment, vitreous hemorrhage, and endophthalmitis.[5,6] Furthermore, while intravitreal administration of corticosteroids has been shown to reduce edema and improve or at least stabilize visual acuity, these effects are often transient.[3] For example, a systemic review of four randomized clinical trials comparing intravitreal triamcinolone acetonide (IVTA) injection with placebo or no treatment found that patients receiving IVTA had a greater improvement in visual acuity at 3 months, but the benefit was no longer significant

at 6 months.[7] This lack of long-term efficacy for a disease that is chronic in nature, 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.

One such steroid drug delivery system in development for use in DME is the dexamethasone intravitreal implant (Ozurdex), which is currently FDA-approved for the treatment of macular edema following retinal vein occlusion. A 2007 study found that the dexamethasone implant improved visual acuity for up to 6 months, and macular thickness and fluorescein leakage for up to 3 months, following implantation in patients with persistent macular edema due to a variety of causes including diabetic retinopathy, retinal vein inclusion, uveitis, and Irvine-Gass syndrome.[8] In a subgroup analysis of 171 eyes with persistent DME, 700 µg of dexamethasone (n=53) was well tolerated and produced statistically significant improvements in best corrected visual acuity and central retinal thickness at day 90. At day 180, however, no significant difference in visual acuity was found between groups (central retinal thickness was not evaluated at day 180), and both treatment groups (350 µg and 700 µg) had an increased incidence of elevated IOP.[9]

Another potential new steroid delivery system is the sustained release fluocinolone acetonide nonbiodegradable intravitreal insert (Iluvien). This insert is designed to release drug for 24 to 36 months from a rod 3.5 mm long and 0.37 mm in diameter, which is delivered using a proprietary device with a 25-gauge needle that creates a self-healing wound.[10]

The two ongoing pivotal multicenter trials known collectively as the FAME study include a total of 956 randomized patients assigned to receive either a low-dose (0.19 mg total, approximately 0.23 µg/day) fluocinolone acetonide insert, a high-dose (0.19 mg total, approximately 0.45 µg/day) insert, or a sham injection. Preliminary results show that 26.8% of low-dose patients and 26.0% of patients receiving a high-dose insert had an improvement in best corrected visual acuity (BCVA) of 15 or more letters in one phase 3 study at 24 months postinsertion.[10] In the other phase 3 study at 24 months, 15 or more letter BCVA improvement was seen in 30.6% of low-dose subjects and 31.2% of high-dose subjects. At 30 months, preliminary analysis looking at both trials combined data shows a 15 or greater letter BCVA improvement in 39.8% of patients (n=123) receiving the low-dose insert.[11] Following the release of results from the two phase 3 studies, a new drug application including the 24-month low-dose data was submitted to the FDA.[12]

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Another emerging treatment is a sustained release triamcinolone acetonide (TA) implant (I-vation), which has completed a phase 1 trial for use in long-term treatment of DME.[13] Although TA is widely used off-label in the management of ocular disorders characterized by edema and inflammation, it is not currently FDA approved for ophthalmic use.[14]

The intrascleral TA micro-implant has a unique helical shape designed to maximize surface area for drug delivery. It is composed of biodegradable polymers that gradually degrade over time, thereby eliminating the risk of secondary surgical complications upon removal, which are often seen with nonbiodegradable devices.[14] In the phase 1 study, 64% of patients receiving a slow-release implant (n=11, approximately 1-3 µg TA/day) and 72% of patients receiving a fast-release implant (n=14, approximately 3-5 µg TA/day) demonstrated improved visual acuity at 24 months.[15] However, both groups experienced a rise in mean intraocular pressure with an increase from 13.9 mm Hg at baseline to 16.6 mm Hg in the slow group and from 14.3 mm Hg to 15.9 mm Hg in the fast-release group.[15]

ANGIOGENESIS INHIBITORS

In addition to steroids, researchers are also exploring more specific antiangiogenic agents in an effort to address the leakage and, perhaps, neovascularization associated with DME. The most popular target of these agents is the subfamily of proteins known as VEGF, whose overexpression is believed to play a role numerous diseases including DME and age-related macular degeneration (AMD).[16,17]

Notably, the latest results of the Diabetic Retinopathy Clinical Research Network (DRCR.net) were presented recently, examining the efficacy of ranibizumab, a monoclonal antibody fragment that binds to and inhibits VEGF-A. Ranibizumab (Lucentis), which is currently FDA-approved for the treatment of wet AMD, and its sister antibody bevacizumab are also used off-label to treat leakage and neovascularization in DME.

In the DRCR.net study, patients with DME involving the fovea were randomized by eye to one of four treatment groups: 0.5 mg intravitreal ranibizumab with prompt focal/grid laser photocoagulation (n=187 eyes),

ranibizumab with deferred (at least 24 weeks) laser (n=188), 4 mg IVTA with prompt laser (n=186), or a sham injection with prompt laser (n=293).[18] At 1-year evaluations, 0.5 mg intravitreal ranibizumab combined with either prompt or deferred laser photocoagulation demonstrated superior efficacy in BCVA (nine letter gain for both groups) and optical coherence tomography (OCT) endpoints compared with laser treatment alone (three letter gain), with similar results shown after 2 years. In contrast, IVTA combined with laser did not result in superior BCVA outcomes (four letter gain) compared with laser alone, but did result in greater reduction in retinal thickening measured with OCT at 1 year but not 2 years vs laser alone. Interestingly, among the subset of patients that were pseudophakic at baseline, the IVTA group experienced a level of visual improvement similar to the ranibizumab group, suggesting that the lesser improvement on BCVA observed in the whole IVTA group may be the result of cataract development in baseline phakic patients.[18]

In addition to the positive news from the DRCR.net, interim results of a large ongoing multicenter phase 2 study evaluating the efficacy and safety of VEGF trap (VEGF Trap-Eye) in patients with DME have recently been presented.[17] VEGF trap is a soluble VEGF receptor fusion protein that binds to all isoforms of VEGF-A and placental growth factor, another growth factor upregulated during neovascularization. After 24 weeks in the phase 2 study, patients who received VEGF trap 0.5 mg monthly (n=44) exhibited a mean increase of 8.6 letters in BCVA, those who were given VEGF trap 2 mg monthly (n=44) had an 11.4 letter mean gain in BCVA, while those receiving VEGF trap 2 mg as-needed following 3 monthly injections had a 8.5 letter mean increase. By comparison, patients who received laser therapy (n=44, average of 1.7 treatments) exhibited a mean 2.5 letter gain in BCVA.[19]

Pegaptanib sodium (Macugen) is also being investigated as an anti-VEGF agent for DME. Notably, results from a double-blind phase 3 study comparing pegaptanib sodium to sham injection in a total of 260 patients with DME were recently presented at the World Ophthalmology Congress in Berlin. For the first year of the trial, subjects received an injection of 0.3 mg pegaptanib or a sham procedure every 6 weeks for a total of nine injections. In the second year, subjects were given an injection on an as-needed basis as frequently as every 6 weeks based on prespecified criteria. After 54 weeks, 37% of patients in the pegaptanib group gained at least two lines in BCVA compared with 20% in the sham group. By the end of year 2, subjects receiving pegaptanib gained an average of 6.1 letters in BCVA, while those receiving sham injection had a mean increase of 1.3 letters.[20]

SUMMARY

There is no shortage of exciting news from researchers searching for an effective pharmaceutical treatment for DME. Promising new antiangiogenic and antiinflammatory therapies may soon offer hope to diabetic patients. ■

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