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Evolution of intravitreal therapy for retinal and macular disorders

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Macular diseases include a variety of complex pathologies, such as age-related macular degeneration (AMD), diabetic macular oedema (DMO), and macular oedema secondary to retinal vein occlusion (RVO), all of which can lead to potential permanent severe visual loss. Early diagnosis and treatment are essential to prevent blindness and maintain quality of life. In this short historical review, the evolution of modern intravitreal treatment for retinal and macular diseases is presented.

The macula (also known as the macula lutea) is the central area of the retina and consists of cone photoreceptors. Direct exposure of the macula to light provides the centre of the visual field.[1] The structure of the macula must be undisturbed and dry to provide clear images to the brain and maintain good vision. Therefore, any disorder that affects the structure of the macula is considered sight-threatening and must be treated both efficiently and promptly.

During the first decades of the 20th century, the treatment of retinal and macular disorders was relatively conservative and limited to oral or local medication. In 1920, Jules Gonin in Lausanne, Switzerland performed the first successful treatment of retinal detachment by sealing the retinal break to the underlying retinal pigment epithelium and the choroid.[2] Robert Machemer performed the first pars plana vitrectomy in 1970.[3] Additionally, retinal laser photocoagulation was introduced in the 1950s by Gerhard Meyer-Schwickerath and Hans Littmann of Zeiss Laboratories.[4] In the 1980s and 1990s, intravitreal injections of antibiotics were increasingly used to treat intraocular infections; thus, ophthalmologists became very familiar with intravitreal administration of drugs.[5,6]

In the 1980s and 1990s, as the acquired immunodeficiency syndrome (AIDS) epidemic unfolded, cytomegalovirus (CMV) infection, along with its most obvious

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clinical presentation, CMV retinitis, became the most common opportunistic infection in AIDS patients.[7] These patients were, initially, treated with intravenous ganciclovir, which showed limited therapeutic effect and increased the risk of sepsis because of the required indwelling catheter. In an effort to overcome these limitations, some ophthalmologists began to use intravitreal injections of ganciclovir for CMV retinitis, which were given on a weekly basis due to the short intravitreal half-life.[8,9] This approach proved highly effective; however, as AIDS-related co-morbidities increased, clinic visits and injections were sometimes missed, leading to suboptimal management. To improve treatment for these patients, a sustained-release ganciclovir implant was developed.[10,11] The ganciclovir implant was approved by the Food and Drug Administration (FDA) in March 1996; it was significantly more effective, compared with classical systemic treatment, dramatically reducing the incidence of CMV retinitis during the latter half of the 1990s.[12–15]

Following the ganciclovir implant, a sustained-release fluocinolone drug delivery device was approved by the FDA for the treatment of severe posterior uveitis.[16–18] This implant was proven to be efficient in patients with persistent DMO, leading to complete resolution of the fluid in some cases; this effect had not been previously observed.[19] This observation showed the potential therapeutic effect of steroids for cases of DMO and led ophthalmologists to begin injecting triamcinolone into the vitreous cavity with excellent results, which were later confirmed by randomized clinical trials.[20,21] The use of intravitreal triamcinolone was later expanded to include RVO-related cystoid macular oedema (CMO), uveitic macular oedema, and Irvine-Gass Syndrome.[22–24]

In the 1990s, several studies showed that vascular endothelial growth factor (VEGF) was present at high levels in the neovascular membranes of patients with wet AMD and that drugs which could inhibit VEGF might provide a possible treatment for choroidal neovascularisation.[25–27] In 2004, Pegaptanib (Eyetech Pharmaceuticals and Pfizer) became the first anti-VEGF agent to receive approval by the FDA for the treatment of neovascular AMD.[28] Soon after, bevacizumab (Genentech and Roche) was approved for cancer therapy; given the role of VEGF in wet AMD, intravenous and later intravitreal administration of bevacizumab was offered to patients with neovascular AMD as off-label treatment.[29] Ranibizumab (Genentech and Novartis), a humanized monoclonal anti-Fab antibody that binds with high affinity to VEGF-A and inhibits all of its biologically active isoforms, was found to be an effective and safe treatment for neovascular AMD in two pivotal trials, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) in 2006.[30,31] Based on this evidence, ranibizumab received FDA approval the same year and became the gold standard for the treatment of wet AMD.[32,33] In the 2010s, a number of trials showed that ranibizumab was also an effective treatment for other macular diseases, including DMO and RVO-related CMO.[34–38] Concurrently, Ozurdex (dexamethasone intravitreal implant releasing steroid continuously over a 3–6 month period), developed by Allergan Inc., received FDA approval for the treatment of macular oedema secondary to central and branch RVO.[39,40] Clinical trials showed that Ozurdex is also an efficient treatment for DMO, non-infectious intermediate and posterior uveitis, and postoperative macular oedema.[41–43] Today, Ozurdex implant is mainly used as first-line treatment for macular oedema secondary to diabetes

and RVO or second-line treatment when anti-VEGF agents fail, especially in pseudophakic patients and patients without history of glaucoma, as steroids will accelerate cataract progression and can eventually increase intraocular pressure.[44,45]

In 2011, the FDA approved aflibercept/VEGF trap (Bayer HealthCare, Inc., and Regeneron Pharmaceutical, Inc.), a recombinant fusion protein that inhibits VEGF-A, VEGF-B, and placental growth factor, for the treatment of neovascular AMD.[46] The most important advantage of aflibercept, compared with ranibizumab and bevacizumab, is the need for less-frequent injections.[47–49] VEGF trap was also found to be an efficient treatment for DMO and RVO-related CMO, showing better functional improvement in cases with worse visual acuity at baseline, compared with ranibizumab and bevacizumab.[50–53] In 2014, Iluvien (intravitreal implant releasing fluocinolone acetonide for 36 months), developed by Alimera, received FDA approval for DMO and has been shown to be effective for patients who have persistent or recurrent macular oedema, despite previous multiple and frequent anti-VEGF injections.[54,55] Recently, brolucizumab, a new anti-VEGF agent for the treatment of wet AMD (developed by Alcon Laboratories, Inc.), has been found to be comparable to aflibercept, with better anatomical results.[56] Larger studies in this field, especially regarding the efficacy of the newer anti-VEGF drug, brolucizumab, are expected with great interest.

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