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Advances in intravitreal therapy and implants: where are we now?

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“The development of intravitreal drugs and intraocular implants has revolutionized the treatment of retinal and macular diseases.”

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Vitreous and retinal diseases include a variety of complex pathologies, such as diabetic retinopathy, retinal vein occlusions (RVO), age-related macular degeneration (AMD), vitreomacular traction, epiretinal membranes, intraocular inflammations and infections, all of which can lead to irreversible severe visual loss. Prompt diagnosis and proper treatment are of utmost importance for patients' vision and quality of life.

History & recent advances

During the last two decades of the 20th century, intravitreal administration of antibiotics for the treatment of intraocular infections increased significantly [1]. Moreover, during the same period, the AIDS epidemic spread all over the world and, consequently, cytomegalovirus (CMV) retinitis incidence increased in the context of CMV infection, which is the most common, opportunistic, infection of the syndrome [2]. Due to the limited therapeutic effect of intravenous ganciclovir in CMV retinitis, intravitreal ganciclovir injections became the standard treatment as they proved to be highly effective [3]. Soon, a sustained-release ganciclovir implant, Vitrasert® by Bausch & Lomb (NJ, USA), was developed and approved by the US FDA in 1996 in order to improve the treatment of individuals with CMV retinitis, leading to a dramatic reduction of CMV retinitis incidence [4]. In 2005, the FDA approved a sustained-release fluocinolone 0.59 mg drug-delivery device, Retisert® by Bausch & Lomb for the treatment of severe posterior uveitis [5]. Apart from being an efficient treatment for CMV retinitis, Retisert was demonstrated to be efficient for individuals with chronic diabetic macular oedema (DMO) as well, resulting in complete resolution of the fluid in many cases [6]. Following this observation and in view of the potential therapeutic effect of steroids on DMO, intravitreal administration of triamcinolone supplemented the traditional macular laser with excellent results for individuals with DMO and was also very efficient in individuals with uveitic, postoperative and RVO-related macular oedema (MO) [7–10].

In 2004, the FDA approved the anti-VEGF agent pegaptanib by Eyetech Pharmaceuticals and Pfizer (NY, USA) for the treatment of exudative AMD [11]. Also, in 2004 bevacizumab by Genentech (CA, USA) and Roche (Basel, Switzerland) was approved for cancer therapy and offered to individuals with neovascular AMD as an off-label therapy, initially as intravenous and later as intravitreal treatment [12]. Following the results of MARINA and ANCHOR trials, ranibizumab by Genentech and Novartis (Basel, Switzerland), a monoclonal anti-antibody fragment that blocks VEGF-A and all of its biologically active isoforms, received FDA approval in 2006 and became the most widely used treatment for the neovascular AMD [13,14]. In 2011, aflibercept or VEGF trap by Bayer HealthCare, Inc. (Berlin, Germany) and Regeneron Pharmaceutical, Inc. (NY, USA), a recombinant fusion protein that inhibits VEGF-A, VEGF-B and placental growth factor, became the third anti-VEGF agent to receive FDA approval for the treatment of wet AMD [15]. During the last decade, a number of studies demonstrated that both ranibizumab and aflibercept were also very effective therapeutic options for other macular conditions, such as DMO and RVO-related MO [16–20]. However, the advantage of aflibercept compared with ranibizumab and

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bevacizumab is the need for less-frequent injections in individuals with AMD and better functional improvement in cases with severe visual acuity loss at baseline, in individuals with DMO and RVO [15,21–23]. Concurrently, the intravitreal steroid implant, Ozurdex® by Allergan Inc (Dublin, Ireland), received FDA approval initially for the treatment of RVO-related MO in 2009 and for the treatment of noninfectious ocular inflammation and DMO in 2010 and 2014, respectively [24–27]. In 2012, ocriplasmin 125 µg injection, Jetrea® by ThromboGenics NV (Leuven, Belgium), received FDA approval for the treatment of symptomatic vitreomacular adhesion; however, up to 20% of eyes treated with Jetrea will still require additional treatment with vitrectomy and in view of the few studies that have been conducted, there is a controversy regarding the advantages and disadvantages of ocriplasmin [28]. In 2014, FDA approved the fluocinolone acetonide 0.19 mg sustained intravitreal implant, Iluvien® by Alimera (GA, USA), for the treatment of DMO, refractory to conventional treatment following the results of FAME trials [29,30]. Iluvien was found to be a safe and efficient therapeutic option for this group of individuals with DMO, achieving resolution of persistent or recurrent DMO and improving visual acuity, while simultaneously reducing the need for injections and frequency of hospital visits [31]. Moreover, two recent case reports revealed the efficacy of Iluvien in patients with persistent noninfectious uveitis with co-existing macular oedema [32,33]. In October 2018, the FDA approved another steroid implant, YUTIQ by EyePoint Pharmaceuticals (MA, USA), which contains 0.18 mg fluocinolone acetonide and is designed to release 0.25 mcg/day over a period of 36 months for the treatment of chronic posterior uveitis. YUTIQ was found to be efficient in reducing recurrence of uveitis, resolving MO and improving vision without significant adverse events [34].

Another intraocular drug-delivery system that allows sustained release of small dexamethasone molecules is DEXYCU by Icon Biosciences, Inc (MA, USA) and was approved in 2018 for the treatment of postoperative inflammation [35].

Current & future advances

In October 2019, the newer anti-VEGF agent, brolucizumab/RTH258, developed by Alcon Labs (Geneva, Switzerland) and Novartis (Basel, Switzerland), was approved by the FDA for the treatment of wet AMD, following the results of HAWK and HARRIER trials, which demonstrated that brolucizumab was as efficient as aflibercept in terms of visual function; however, in terms of anatomic outcomes, brolucizumab was found to be superior [36].

Earlier this year (2019), conbercept by Lumitin, Chengdu Kang Hong Biotech (Sichuan, People's Republic of China), a new anti-VEGF agent, already approved in China for the treatment of wet AMD, was reported to be an efficient and safe treatment with a dosing regimen of three initial monthly administrations followed by quarterly injections, according to the PHOENIX study [37]. The results of PANDA-1 and PANDA-2 trials (NCT03577899 and NCT03630952, respectively), which will compare two doses of conbercept (0.5 and 1.0 mg) to 2.0 mg aflibercept are expected to have great interest in 2020.

KSI-301 by Kodiak Sciences (CA, USA) is a novel, anti-VEGF antibody biopolymer conjugate for the treatment of wet AMD and other macular diseases. A Phase Ib trial (NCT03790852) in treatment for individuals with naive eyes and neovascular AMD, DMO and RVO-related MO is currently ongoing and the first results are expected in 2020 [38].

Faricimab, by Roche and Genentech, is a bispecific antibody targeting both VEGF-A and angiopoietin-2 promising to reduce treatment load and improve functional outcomes in individuals with neovascular AMD and DMO. Faricimab is, currently, in Phase III trials (LUCERNE, NCT03823300) and the results are expected in August 2021 [39].

Three intraocular drug-delivery implants are currently in clinical trials.

The brimonidine tartrate intravitreal implant, Brimo PS DDS, by Allergan, for the treatment of AMD geographic atrophy is currently in Phase II clinical trials (NCT01080209) [35].

The ranibizumab port delivery system, by Genentech and ForSight Vision4 (CA, USA) is a nonbiodegradable, refillable reservoir device that delivers ranibizumab for the treatment of neovascular AMD and is currently in Phase III trial (NCT03677934), following the results of the Phase II Ladder Clinical Trial, which demonstrated that visual and anatomic outcomes of individuals treated with port delivery system were comparable to monthly intravitreal ranibizumab injections, but with less ranibizumab treatments [40].

OTX-IVT, by Regeneron and Ocular Therapeutix (MA, USA), is a sustained release formulation of aflibercept, which intends to reduce the frequency of injections to once every 4–6 months and is currently undergoing clinical evaluation in the USA [35].

Conclusion

The development of intravitreal drugs and intraocular implants has revolutionized the treatment of retinal and macular diseases. Anti-VEGF medications such as bevacizumab, ranibizumab and aflibercept and intravitreal implants such as Ozurdex and Iluvien are widely used and have significantly reduced the incidence of severe visual loss caused by AMD, DMO, RVO and ocular inflammations. Drugs in the pipeline such as the new sustained-release implants described above and the new anti-VEGF agents (combined with Tie-2 receptor modulator) are expected to have great interest. Moreover, gene therapy seems to be a promising therapeutic option in the future aiming for continuous production of anti-angiogenic proteins via the retina's own cell [41].

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