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Cover story

Ocular microparticle formulations for 6-month delivery of anti-VEGF

Dr. Judah Folkman's groundbreaking research in the fields of angiogenesis and vascular biology has been translated into successful medicines in the eye to treat disorders, such as wet age-related macular degeneration (AMD) and diabetic retinopathy. Although preceded by the ill-fated aptamer, pegaptanib (Macugen), the development of ranibizumab (Lucentis), the first protein-based vascular endothelial growth factor (VEGF) inhibitor for wet AMD, was the most significant and revolutionary [1]. These VEGF inhibitors are administered by intravitreal (IVT) injection, locally into the eye. While Lucentis is highly effective, it is also highly expensive. Efforts have been focused on using cheaper alternatives, led by the off-label use of bevacizumab (Avastin), a full antibody VEGF inhibitor developed for cancer, as well as on finding drugs and drug formulations that would extend the efficacy to several months. The more potent and longer acting aflibercept (VEGF Trap-eye, Eylea), another biologic, with an extended label of bi-monthly administration is now becoming the leading VEGF inhibitor for wet AMD treatment by IVT injection [2].

The challenge to extend the efficacy of a VEGF inhibitor to several months or longer has become a 'holy grail' in the controlled release field. The paper by Dr. Ian R. Catchpole and his team in this issue has addressed some of the many challenges of delivering an active anti-VEGF biologic in a controlled release system over 6 months in the eye of a non-human primate (NHP) [3]. The work demonstrates that it is possible to load microparticles with sufficient amounts of a potent anti-VEGF molecule and inject IVT to sustain release over 6 months in the NHP at sufficient levels to protect against laser choroidal neovascularisation (CNV), the pre-clinical model of wet AMD. The approach was modelled to predict clinical efficacy in man.

Despite this considerable success, the work highlights further challenges to overcome before long-acting microparticle formulations could be used in man. It is still difficult to find an ideal delivery system that could provide high drug loading capacity, a stable environment for protein, minimal initial burst release followed by a steady state release over 6 months, and a degradation kinetics that matches the release rate. The limited intravitreal volume cannot afford additional doses without timely degradation of the previous delivery system. Ocular inflammation in response to injection of particulates is something expected. One unexpected observation in the study, however, was particle migration from the vitreous to the anterior chamber of the eye in the primate. This finding appears to be related to the ocular biology of primate and man, and was not seen in the many rabbit studies performed by the authors and many other scientists. The paper highlights the risks that could be directly applicable to other particle based delivery systems for IVT administration. It shows the need for the use of a NHP model as a validation of such systems.

Intravitreal injection to the eye has been an attractive application for controlled release technologies to exploit the small vitreal volume (4.5 ml in man), as an enclosed environment to enable locally administered drug efficacy. If the issues highlighted by Dr. Catchpole and his colleagues cannot be resolved for particulate systems in the eye, then other approaches will need to be considered. Thermo-sensitive injectable solidifying gels offer an alternative, if they can provide controlled release of a VEGF inhibitor for several months. Gene therapy via sub-retinal and IVT injection of both adeno-associated viral and lentiviral vectors is starting to show long-term success in man. Such an approach may offer a single administration to control ocular diseases, although long term efficacy and safety data is awaited. Controlled release systems can deliver efficacious biologics for months, but numerous challenges are ahead for successful clinical applications. The importance of the work by Dr. Catchpole and his team is that it clearly describes the difficulties associated with developing 6-month biologic delivery systems with unexpected observations, such as microparticle migration, paving the way to find solutions. Without knowing the problems clearly, the right answers cannot be found. We need more articles like the one by Dr. Catchpole and his coworkers describing the problems, difficulties, and challenges for us to move forward towards finding clinically useful formulations.

References

[1] N. Ferrara, L. Damico, N. Shams, H. Lowman, R. Kim, Development of ranibizumab, an anti–vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration, Retina 26 (2006) 859–870.
[2] J.S. Heier, D.M. Brown, V. Chong, J.F. Korobelnik, P.K. Kaiser, Q.D. Nguyen, B. Kirchhof, A. Ho, Y. Ogur, G.D. Yancopoulos, N. Stahl, R. Vitti, A.J. Berline, Y. Soo, M. Anderesi, G. Groetzbach, B. Sommerauer, R. Sandbrink, C. Simader, U. Schmidt-Erfurth, VIEW 1 and VIEW 2 Study Groups, Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration, Ophthalmology 119 (2012) 2537–2548.
[3] P. Adamson, T. Wilde, E. Dobrzynski, C. Sychterz, R. Polsky, E. Kurali, R. Haworth, C.M. Tang, J. Korczynska, F. Cook, I. Papanicolaou, L. Tsikna, C. Roberts, Z. Hughes-Thomas, J. Walford, D. Gibson, J. Warrack, J. Smal, R. Verrijk, P.E. Miller, T.M. Nork, J. Prusakiewicz, T. Streit, S. Sorden, C. Struble, B. Christian, I.R. Catchpole, Single ocular injection of a sustained-release anti-VEGF delivers 6 months pharmacokinetics and efficacy in a primate laser CNV model, J. Control. Release 244 (2016) 1–13.

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