Journal of Controlled Release 266 (2017) 365

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Tolerance levels of PLGA microspheres in the eyes

Diseases affecting the posterior segment of the eye are one of the major causes of blindness in the elderly population. Most of these pathologies are chronic and successful treatments require frequent administration of the active substance to maintain effective concentrations in the intraocular target site. This requires repeated intraocular injections causing significant inconvenience to patients. Successive intravitreal administrations are also related to adverse effects such as cataracts, retinal detachment, and hemorrhage, among others. Furthermore, the risk of the side effects increases with the number of injections [1]. Long acting intraocular drug delivery systems are attractive therapeutic tools in the treatment of posterior segment diseases.

Ocular drug delivery systems can be classified as implants, microparticles, and nanoparticles. The most widely used biodegradable polymers are poly(lactide-co-glycolide) (PLGA) with varying ratios of the lactide and glycolide contents. PLGA-based microparticle formulations have become popular in treating posterior segment diseases over the last few years [2]. For long-term treatment the depot formulations need to provide intraocular tolerance. PLGA microparticles have been used in a few dozen long-acting depot formulations, but no ocular microparticle formulation has been approved by the United States Food and Drug Administration (US FDA). Only one PLGA solid implant formulation is currently used for up to 6-month delivery of dexamethasone in the eye. It is important to evaluate the *in vivo* response of blank (i.e., with no drug or unloaded) PLGA microspheres. The collaborative paper of Professors Francine Behar-Cohen and Rocío Herrero-Vanrell and their team deals with the intraocular delivery of spironolactone, a mineralocorticoid antagonist (MRA), from PLGA microspheres [3]. The eye is a mineralocorticoid (MR) sensitive organ and an over-activation of MR by excess glucocorticoid or endogenous activation has been hypothesized in the pathogenesis of central serous chorioretinopathy (CSCR) [4]. Long-term systemic use of spironolactone is known to be associated with hormonal side effects, such as gynecomastia, menstrual irregularities, and erectile dysfunction, in particular with the CSCR population consisting mostly of middle-aged men [5]. Optimized MR blockade with reduced side effects requires intraocular local MRA delivery using sustained release depot formulations.

The study by the Behar-Cohen/Herrero-Vanrell team presents interesting findings [3]. The high intravitreal concentration of PLGA microspheres (10 mg/mL), regardless of the presence of spironolactone, induced retinal stress and photoreceptor dysfunction in rats. The lower microsphere concentration of 2 mg/mL, however, showed excellent morphologic and functional tolerance in rats. In the absence of a mechanistic understanding of this phenomenon, the use of a lower concentration of PLGA microspheres is a safer therapeutic choice for chorioretinal disorders in which illicit MR activation could be pathogenic. While the study was limited to testing only two different concentrations of PLGA microspheres, the work is significant for several reasons.

Most of the PLGA microspheres are characterized for their drug loading and release properties. There are not many research articles describing the *in vivo* impact of PLGA microspheres themselves. The observation that the same PLGA microspheres may elicit undesirable effects in the eye depending on the microsphere concentration suggests a few design parameters to consider. First, there is a need to increase the drug loading so that the larger amounts of drug can be delivered for more than a month. This requires further advances in our understanding of PLGA microsphere preparation, e.g., increased drug loading with reduce initial burst and longer steady state release. Second, the toxicities observed in animal studies of ocular PLGA microsphere formulations may be reexamined, as the side effects can be reduced or eliminated by using lower concentrations of the microspheres. Third, PLGA microspheres may have different *in vivo* toxicities depending on the size of microspheres. Since the mechanisms of the PLGA microsphere concentration effects are not known, there is a need to understand whether the effect of the microsphere concentration is due to the total amount of PLGA or the surface area of the microspheres. If the latter is a factor, then careful selection of the microsphere size becomes a critical factor. As the microsphere size increases (to the extent that can still be injected through a 30 gauge needle), the number will decrease and it may increase the functional tolerance. The work by the Behar-Cohen/Herrero-Vanrell team is simple and yet highly elegant in concept. Such a new approach of evaluating the functions of PLGA microspheres will undoubtedly accelerate the clinical translation of long-acting PLGA formulations.

References

[1] R. Herrero-Vanrell, M.F. Refojo, Biodegradable microspheres for vitreoretinal drug delivery, Adv. Drug Deliv. Rev. 52 (1) (2001) 5–16.
[2] R. Herrero-Vanrell, I. Bravo-Osuna, V. Andres-Guerrero, M. Vicario-de-la-Torre, I.T. Molina-Martinez, The potential of using biodegradable microspheres in retinal diseases and other intraocular pathologies, Prog. Retin. Eye Res. 42 (2014) 27–43.
[3] M. Zhao, E. Rodríguez-Villagra, L. Kowalczuk, M. Le Normand, M. Berdugo, R. Levy-Boukris, I. El Zaoui, B. Kaufmann, R. Gurny, I. Bravo-Osuna, I.T. Molina-Martínez, R. Herrero-Vanrell, F. Behar-Cohen, Tolerance of high and low amounts of PLGA microspheres loaded with mineralocorticoid receptor antagonist in retinal target site, J. Control. Release 266 (2017) 187–197.
[4] M. Zhao, I. Célérier, E. Bousquet, J.C. Jeanny, L. Jonet, M. Savoldelli, O. Offret, A. Curan, N. Farman, F. Jaisser, F. Behar-Cohen, Mineralocorticoid receptor is involved in rat and human ocular chorioretinopathy, J. Clin. Invest. 122 (7) (2012) 2672–2679.
[5] A. Daruich, A. Matet, A. Dirani, E. Bousquet, M. Zhao, N. Farman, F. Jaisser, F. Behar-Cohen, Central serous chorioretinopathy: Recent findings and new physiopathology hypothesis, Prog. Retin. Eye Res. 48 (2015) 82–118.

Kinam Park
Purdue University
Biomedical Engineering and Pharmaceutics
West Lafayette, IN 47907, USA
E-mail address: kpark@purdue.edu

https://doi.org/10.1016/j.jconrel.2017.11.010