Novel photocrosslinked anti-VEGF loaded ocular Implants

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Background:

Photocrosslinked systems have been deployed in a range of diverse applications with tremendous success over the past few decades [1]. In terms of drug delivery, it has been demonstrated that photocrosslinked systems provides protein release for markedly extended periods [2]. Intravitreal injection of bevacizumab (BEZ) is routinely used in patients with neovascular age-related macular degeneration (AMD) despite the fact that it is not approved for the treatment of eye illnesses by Food and Drug Association (FDA). However, since intravitreal administration is an invasive method, repeated injections can cause patient intolerance and lead to a range of complications [4]. For this study, we investigated the possibility of using photocrosslinked implants, composed of poly(ethylene glycol) diacrylate (PEGDA) and poly(lactic-co-glycolic acid) (PLGA), for sustained long-term delivery of BEZ with the goal of reducing the number of ocular injections required. An evaluation was performed on the *in vitro* release, the activity of released BEZ, the biocompatibility, and the preclinical effectiveness of the BEZ-loaded implants in VEGF-challenge rabbits.

Methods:

Gel formulation composed of PEGDA, BEZ, PLGA and photoinitiator were injected into silicon moulds and photocrosslinked to produce rod-shaped implants. *In vitro* BEZ release was conducted in PBS at pH 7.4±0.2 and quantified using a validated size exclusion chromatography (SEC) [5]. Activity was assessed using a validated ELISA assay, and biocompatibility was performed on retinal pigment epithelial cells (ARPE-19). Preclinical efficacy and tolerability of the long-acting BEZ-loaded implants were evaluated in a VEGF-challenge rabbit model.

Results:

Optimised implants showed sustained release of BEZ for nearly 6 months, and the ELISA results indicated > 80% activity of the released BEZ. The percentage of ARPE-19 cell viability exposed to direct and in direct contact assay was >80%, indicating that no cytotoxic agent was leaching out from the implants and no implant induced cell toxicity. These results demonstrated that the implants were biocompatible. In the preclinical studies, fluorescein angiography scoring showed similar or better efficacy of a single injection of BEZ-loaded implants to that of frequent Avastin® injections in VEGF-challenge rabbit models during the 6-months of the study. Furthermore, implant tolerability in most observed categories is equal to or surpasses that of bolus Avastin® injection.

Conclusions:

The novel photocrosslinked implants can provide a sustained release of biologics for at least 6 months and maintain its activity. The implants showed good biocompatibility with ARPE-19 cells. Preclinical VEGF-challenge studies showed highly promising efficacy of single-injection BEZ-loaded implants, which was either similar or better than the therapeutic efficacy seen with the frequent intravitreal injections of Avastin® over 6 months.