Poly-ε-Caprolactone Intravitreous Devices: An In Vivo Study

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Purpose. The objective of this study was to evaluate the long-term safety and pharmacokinetic profile of a dexamethasone-loaded poly-ε-caprolactone (PCL) intravitreous implant.

Methods. The PCL devices were prepared by compression and were inserted into the vitreous of pigmented rabbits. At different time points, vitreous samples were retrieved, and dexamethasone concentration was analyzed by high-performance liquid chromatography. The biodegradation of the implants was evaluated by scanning electron microscopy, and the dexamethasone remaining was evaluated at the end of follow-up. Clinical and histologic examinations were performed to evaluate the implant's tolerance.

Results. The PCL implant allows for a controlled and prolonged delivery of dexamethasone in rabbits eyes since it released the drug within the therapeutic range for at least 55 weeks. At 55 weeks approximately 79% of the drug was still present in the implant. Biodegradation study showed that PCL implants degradation is very slow. Clinical and histologic observations showed that the devices were very well tolerated in the rabbit eye.

Conclusions. This study demonstrates the feasibility and tolerance of intravitreous PCL drug delivery systems, which can offer a wide range of applications for intraocular drug delivery because of their controlled and prolonged release over months or even years. (*Invest Ophthalmol Vis Sci.* 2009;50:2312–2318) DOI:10.1167/iovs.08-2969

Polymeric drug delivery systems are essential for achieving an ideal pharmaceutical intervention for the eye at a time when new active compounds are available for retinal diseases treatment. These devices allow for a sustained, prolonged release of drugs, increasing their bioavailability and decreasing potential side effects. Biodegradable polymers have been widely explored for the development of ocular drug delivery systems, as no surgical procedure is necessary to remove them when drug delivery is complete.[1]

In a previous study, poly-ε-caprolactone (PCL) intravitreous implants containing dexamethasone were evaluated in vitro.[2] The developed systems were characterized, and the in vitro drug release, the biodegradation, and short-term tolerance were evaluated in rabbits' eyes. The results showed that 25% of the drug was released in the medium from the implants for a period of 21 weeks, and preliminary observations showed that the device was very well tolerated in rabbits' eyes.

We therefore undertook the present study to determine the long-term safety and pharmacokinetic profile of a dexamethasone-loaded PCL intravitreous implant in the rabbit eye with a view toward its potential anti-inflammatory and/or local use in the prevention or treatment of vitreoretinal disorders.

Materials and Methods

Dexamethasone (MW = 392.5; aqueous solubility at 37°C = 1.0 mg/mL) and PCL (MW ~ 14,000) were purchased from Sigma-Aldrich Co. (Saint-Quentin Fallavier, France). Acetonitrile HPLC grade was purchased from EM Science, Merck KgaA (Darmstadt, Germany). Ultrafiltrated water was obtained from Milli Q plus, Millipore (Billerica, MA). All other chemicals were of analytical grade.

Preparation of Implants Containing PCL and Dexamethasone

The implants were developed according to a technique described by Fialho et al.[2] Briefly, the drug (dexamethasone) and the polymer (PCL) at a ratio of 1:4 were dissolved in a mixture of distilled water and acetonitrile, and the resultant solution was lyophilized (Christ Alpha 1-2 LD; Bioblock Scientific, Illkirch, France). The obtained powder was then compressed in an evacuable KBr dye (Shimadzu, Kyoto, Japan), with a hydraulic press (SSP-10A; Shimadzu) in the form of 13-mm diameter discs. The obtained discs were then cut to form 4.0-mm diameter implants. The mean weight of the intravitreous implants was 20.0 ± 1.0 mg. They were 1.5 ± 0.2 mm in thickness (Fig. 1) and contained 5 mg dexamethasone.

In Vivo Release Kinetics

Animals. Pigmented Fauve de Bourgogne female rabbits weighing from 2 to 3 kg and 10 to 12 weeks of age, were used (Elevage des Pins, Epeigne sur Deme, France). All experiments were conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Rabbits received general anesthesia (50 mg/kg ketamine and 15 mg/kg xylazine intramuscular), and local anesthesia was obtained with oxybuprocaine 0.4%. At the end of the experiments, the rabbits were killed by injection of a lethal dose of pentobarbital.

The animals were divided into two groups. In group 1, devices containing dexamethasone were implanted into the vitreous of one eye of each rabbit (n = 8). In group 2, control rabbits received the intravitreous implant without the drug in one eye (n = 8).

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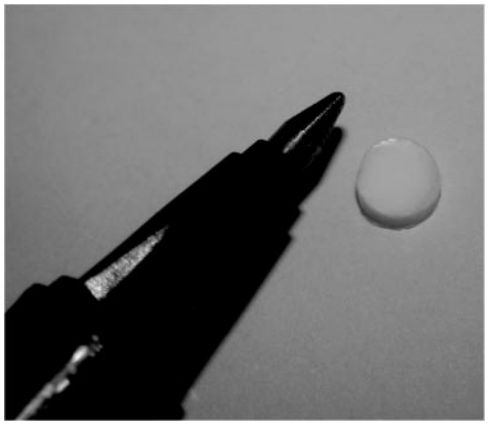

FIGURE 1. Macroscopic picture of the PCL pellet before implantation.

Procedure for Device Implantation. For implantation, the conjunctiva was dissected at the limbus in the temporo-superior quadrant, and a 2-mm sclerotomy was performed 3 mm posterior to the limbus. The PCL implant was inserted through the sclerotomy in the vitreous cavity and the sclerotomy was closed with a 7-0 Vicryl suture. The conjunctiva was reinserted with a 8-0 Vicryl suture. No vitreous bleeding occurred during the procedure.

In the control group, the animals received the implant without drug by the same technique.

At different time points after implantation (1, 7, 13, 18, 25, 32, 41, and 55 weeks), vitreous samples (500 μL) were collected by simple puncture with a 26-gauge needle and 1-mL syringe. Punctures were performed by gentle aspiration after the needle was inserted at 3 mm from the limbus in the nasal superior quadrant and then visualizing the needle in the pupil area. After they were retrieved, the vitreous samples were immediately stored at −80°C until dexamethasone concentrations were determined. The vitreous of the animals of the control group were also retrieved for comparison.

Drug Level Analysis. The amount of dexamethasone released was measured by high-performance liquid chromatography (HPLC) using the method described in the United States Pharmacopeia 29[3] by an HPLC apparatus equipped with an autosampler (model 717 plus; Waters, Milford, MA). A pump (model 515; Waters) was used at a constant flow rate of 1.0 mL/min. A C-18 reverse-phase column (4.6 × 100-mm; macropore size, 2 μm) filled with high-purity silica substantially covered with *n*-alkyl chains (Chromolith RP-18E; Merck KGaA Performance and Life Science Chemicals) was used. The mobile phase was a mixture of acetonitrile and ultrafiltered water (45:55). An ultraviolet detector (model 2487; Waters) was used at a wavelength of 254 nm.

The samples were thawed out at ambient temperature and submitted to analysis in triplicate after homogenization, without previous treatment. The vitreous retrieved from the animals of group 2 was also analyzed as the control.

The validation of the method showed the absence of interference of the incubation medium compounds and the polymer with dexamethasone retention time, discounting the risks of overestimation.

Amount of Dexamethasone Remaining in the Implanted Devices

For the determination of the amount of dexamethasone acetate remaining in the implants at 55 weeks, the retrieved implants were gently washed with distilled water and then dissolved in a fixed volume of acetonitrile. The amount of dexamethasone was measured by using the method described earlier.

Scanning Electron Microscopy Analysis

Morphologic changes on the surface of the dexamethasone-loaded PCL implants retrieved from the rabbits' vitreous were analyzed by scanning electron microscopy (DSM 950 microscope; Carl Zeiss Meditec, Jena, Germany) operating at 15 kV. Retrieved implants after 1 month of implantation and at the end of the follow-up were selected at random. Before visualization, the implants were gently washed with distilled water, blotted with wipes to dry off excess water, and dried for 72 hours in a vacuum desiccator at room temperature. After drying, they were mounted on aluminum stubs. Before microscopic examination, the samples were sputter coated with a gold layer under an argon atmosphere for 1 minute (accessory DSV 203 of the equipment BASF 300; Balzers, Inc., Amherst, NY). The implant surfaces were viewed at 20× to 1000× magnification, and the images were transferred to the computer by means of a digital image transfer interface. Implants not placed within the eye were also analyzed for comparison using the same protocol as described earlier.

Tolerance Study

Clinical Examination. Eyes were observed clinically and photographed at 1 week, and then 1, 2, 3, 6, and 9 months and at the end of follow-up (55 weeks) with special attention to conjunctival hyperemia, intraocular inflammation, cataract, and intraocular pressure. Conjunctival hyperemia was scored according to a modified Draize test[4] as follows: 0, normal vessels; 1, definitely injected vessels; 2, diffuse crimson red, individual vessels not easily discernible; and 3, diffuse beefy red. Intraocular inflammation in the anterior segment was scored according to parameters previously described for experimental uveitis grading,[5] and slightly modified as follows: 0, no inflammation; 1, flare or cells in the anterior chamber with less than 10 cells per slit lamp field in the AC; 2, clinical signs similar to those of grade 3, with many cells in the AC forming a hypopyon or fibrin; and 3 the presence of intense inflammatory reaction in the AC, with total seclusion of the pupil. Posterior segment inflammation was graded as follows: 0, no inflammation; 1, presence of cells or flare in the vitreous but with fewer than 10 cells per slit lamp field in the vitreous; 2, same grading as 1 but with fibrin in the vitreous that impairs visualization of the posterior pole; 3, a dense white vitreous impairing visualization of the fundus in any field.

Histologic Evaluation. At the end of follow-up, the rabbits were killed and the eyes were enucleated for histology. The eyes were fixed in Bouin solution and then opened transversely at 2 mm posterior to the limbus. The implants and the lens were removed, and the remaining posterior segment was embedded in paraffin and sectioned with an autosampler (model 717 plus; Waters) in 7- to 10-μm-thick sections. The sections were stained with hematoxylin-eosin, examined under an inverted microscope (Leica, Heerbrugg, Switzerland), and photographed with a digital camera (Leica).

RESULTS

In Vivo Release Kinetics

Figure 2 shows the mean dexamethasone concentrations released from the drug-loaded PCL devices in the vitreous of the rabbits' eyes during the study period. The drug was released from the implants for 55 weeks within the therapeutic range of 0.15 to 4.00 μg/mL.

Amount of Dexamethasone Remaining in the Implanted Devices

The amount of dexamethasone acetate remaining in the implants at 55 weeks was 3.93 ± 0.71 mg, corresponding to approximately 79% of the total amount of dexamethasone in the device.

Scanning Electron Microscopy Analysis

Figure 3 shows scanning electron photomicrographs of the biodegradable PCL implants loaded with dexamethasone; images were obtained before and after implantation in the rabbits' eyes.

Small changes were observed in the surface of the device after 1 month of implantation. At the end of the follow-up, the degradation was more evident as the number of channels and

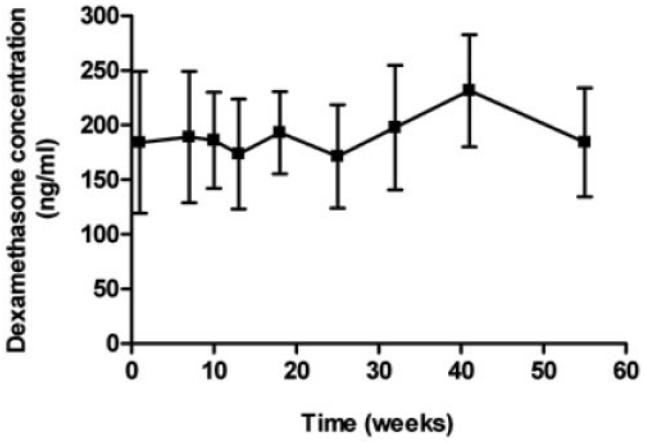

FIGURE 2. Dexamethasone concentrations released from the drug-loaded PCL devices in the vitreous of rabbits' eyes during the study period (mean ± SD).

pores started to increase and the surface showed significant changes.

Tolerance Study

Among the 16 eyes implanted with the PCL device, two developed a severe cataract within the first week (one eye in each group), probably due to surgical trauma. They were removed from the study because it was impossible to follow up the posterior segment anatomy. In two eyes from the control group, we observed an extrusion of the implant at 1 month, when the suture has degraded, with a subconjunctival migration of the implant in one case (Fig. 4A) and a partial extrusion (Fig. 4B) in the other eye, that remained stable throughout the following period. The eye with subconjunctival migration was excluded from the study at 1 month, whereas the other one was kept until the end of the follow-up period. One eye in group 1 showed a dense intravitreous hemorrhage during the follow-up period, because of repeated intravitreous puncture, and was removed from the study. Finally, five eyes in each group were followed up to 55 weeks.

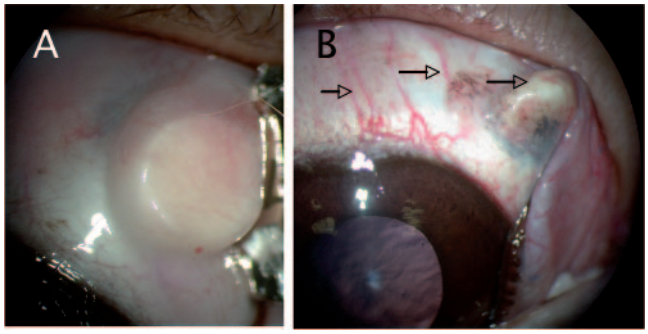

FIGURE 4. Slit lamp photographs of eyes with total extrusion (**A**) or partial extrusion (**B**) of the PCL pellet, at 1 month after implantation. *Arrows* indicate vessel dilation and mild inflammation in the eye with partial extrusion of the implant.

Clinical Examination. *Conjunctival Score.* At 1 week, all eyes had a conjunctival grade of 1. At 1 month, three eyes in the control group (group 2; example shown in Fig. 5A) and one eye in the dexamethasone-loaded group (group 1) had a conjunctival grade of 1, whereas all other eyes were graded 0 (an example is shown in Fig. 5B). Among the three eyes in group 2, one corresponded to the partially extruded implant (Fig. 4B). This eye maintained a grade of 1 throughout the following period, corresponding to localized vasodilatation of conjunctival vessels at the surface and around the implant (Fig. 4B, arrows).

At 1 month and throughout the follow-up period, all eyes in group 1 had a grade of 0 (Fig. 5B). In group 2, at 1 month all

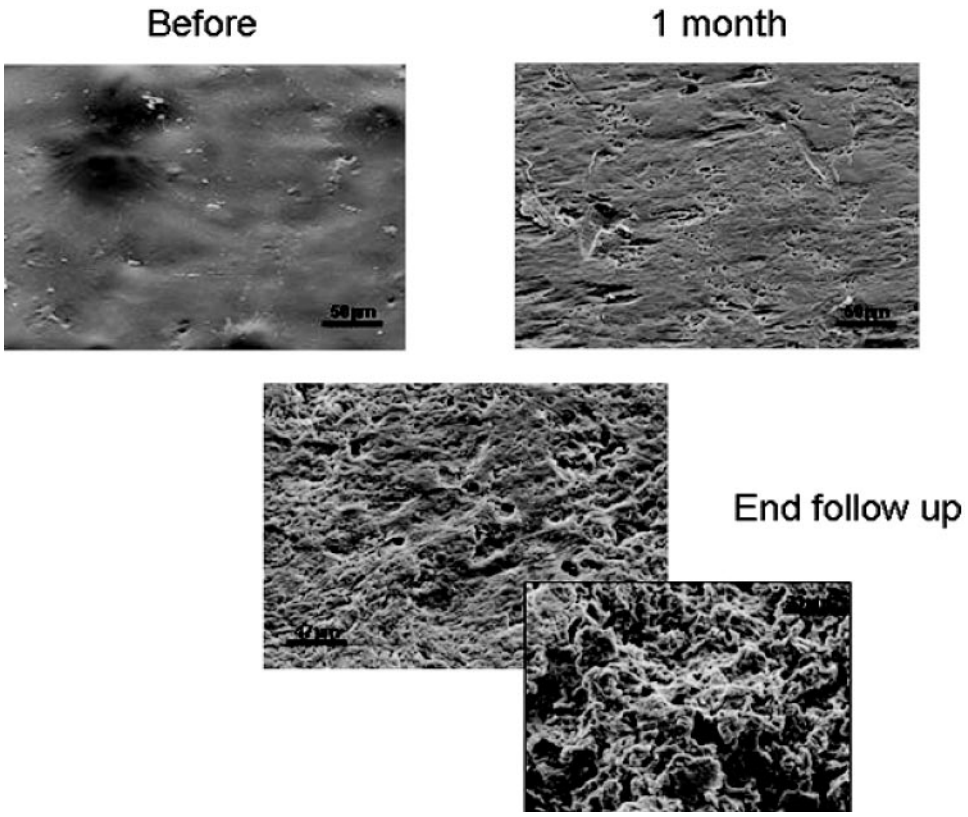

FIGURE 3. Scanning electron photomicrographs of the biodegradable PCL implants loaded with dexamethasone before and after implantation in the rabbits' eyes.

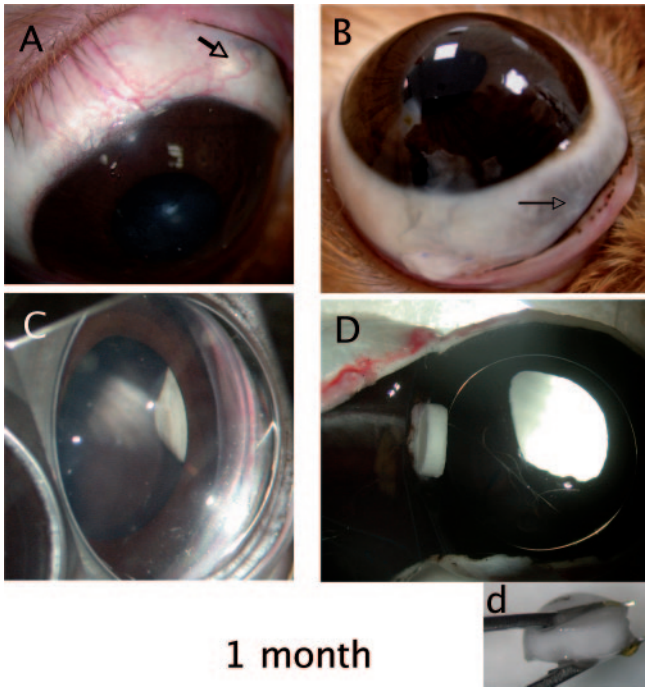

FIGURE 5. Slit lamp photographs of eyes at 1 month after implantation in (**A**) group 2 (PCL alone) with grade 1 inflammation, and in (**B**) group 1 (PCL with dexamethasone) with grade 0. A three-mirror examination allowed visualization of the PCL pellet located at the site of implantation (**C**), whereas direct examination of the interior of the eye after death and enucleation confirmed the presence of the pellet close to the clear lens, at the site of implantation (**D**). The PCL pellet kept its original morphology after 1 month of implantation (**Dd**).

the eyes had a grade of 1 (Fig. 5A), but were grade 0 at all other examination time points.

Anterior Segment Inflammation. None of the eyes at any of the examined time points showed any sign of anterior segment intraocular inflammation. They were all graded 0 in groups 1 and 2.

Posterior Segment Inflammation. None of the eyes in groups 1 and 2 showed any sign of posterior segment inflammation. They were graded 0 in both groups at all the examined time points.

Figure 5 shows examples of posterior segments from eyes in group 1 (three mirrors, Fig. 5C) and in group 2 (direct observation of the vitreous and posterior lens after enucleation, Fig. 5D) at 1 month after implantation. As observed using the three-mirror Goldmann lens, the implant remained at the site of implantation and did not migrate into the vitreous (Fig. 5C), which was confirmed after opening the eyes (Fig. 5D). Similar observation was made in all the implanted eyes.

At 1 month, the PCL implant was still thick (Fig. 5D,d). At the end of follow-up, no signs of inflammation were observed in either group (Figs. 6A, 6B, groups 1 and 2). The PCL implants were partially degraded but were still present in both groups (Figs. 6C, 6D). After the rabbits were killed, the eyes were opened and photographs showed that the PCL implant was stable at the site of implantation and the lens and media were clear (Fig. 6F, example of an eye in group 2). Pictures of the removed implants at this time point confirmed partial degradation with thinning of the implants (Fig. 6G) or partial fragmentation (Fig. 6E). Note that in both groups the implants were still visible, demonstrating that complete degradation did not yet occur.

Intraocular Pressure. In group 1, the mean intraocular pressure in the eye implanted with the dexamethasone-loaded PCL device was 16.2 ± 5 compared with 13 ± 3 in the group 2 eyes implanted with PCL alone ($P = 0.05$). Intraocular pressure was significantly higher in the eye implanted with the dexamethasone-loaded PCL device in group 1, compared with the contralateral, nonimplanted eye (16.2 ± 5 vs. 10.62 ± 3, $P < 0.01$), although there was no significant difference in the mean intraocular pressure of eyes implanted with PCL in group 2, compared with the nonimplanted contralateral eye (13 ± 3 vs. 13.73 ± 3.31, $P > 0.005$).

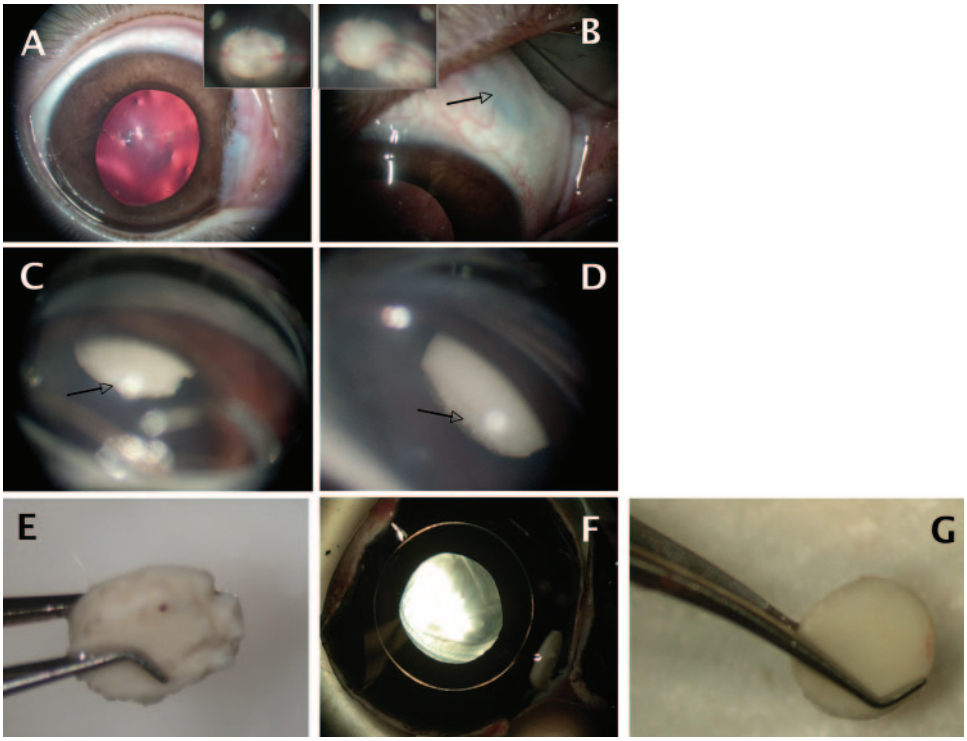

FIGURE 6. Slit lamp photographs at the end of follow-up, showing no sign of inflammation of the anterior segment and at the site of implantation in eyes from groups 1 (**A**), and 2 (**B**). The PCL implants were partially degraded but were still present in eyes from groups 1 (**C**, **E**) and 2 (**D**, **G**). Macroscopic photo of an eye from group 2, sectioned posterior to the lens after enucleation, shows a thin pellet still located at the site of implantation (**F**).

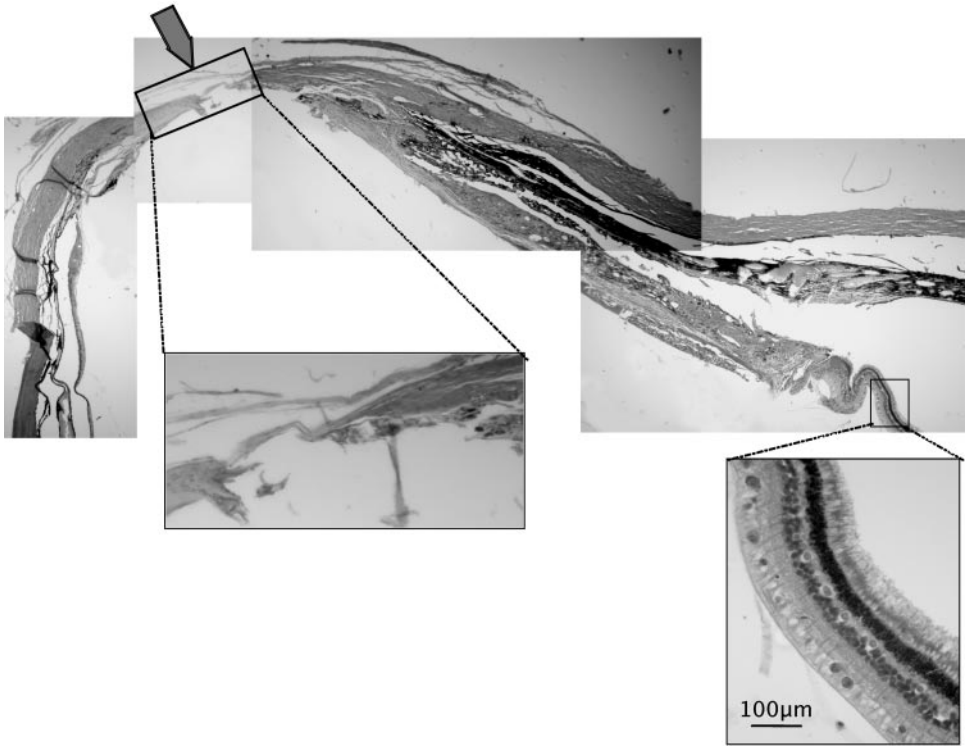

FIGURE 7. Microphotographs of an eye section from group 1, showing intense scleral thinning at the site of implantation (*arrow*) and normal retina structure adjacent to it (*inset*: higher magnification).

Therefore, the sustained release of dexamethasone induced a significant but moderate increase in intraocular pressure in the implanted eyes, but the PCL implant by itself was not responsible for the intraocular pressure increase.

Histologic Evaluation. No gross histologic damage was observed in any of the examined eyes. Particularly, no sign of inflammation (infiltrating cells or fibrin) was observed in group 2 (PCL) compared with PCL dexamethasone (group 1). However, at the site of implantation, the sclera appeared much thinner in group 1 (Fig. 7) compared with group 2 (Fig. 8). Although scleral scaring appeared almost complete in the group 2 eyes (Fig. 7, high magnification), a variable but constant thinning of the sclera was observed in group 1 (Fig. 7 shows the thinner implantation site observed among all eyes in group 1). The retina adjacent to the implantation site appeared normal in both groups (Figs. 7, 8). Therefore, PCL, per se, did not induce any detectable histologic damages, but the slow release of dexamethasone from PCL over a long period induced a thinning of the sclera at the site of implantation.

DISCUSSION

The treatment of diseases affecting the posterior segment tissues of the eye is considerably limited by the difficulty in delivering effective doses of drugs to the vitreous, retina, and choroids through conventional routes of administration.[6] Topical delivery is not effective for administering the more hydro phobic compounds because of their limited intrascleral penetration. The intravitreous injection has to be repeated to maintain the therapeutic level of the agent; such repeated injections have many drawbacks including (1) patient discomfort and noncompliance;

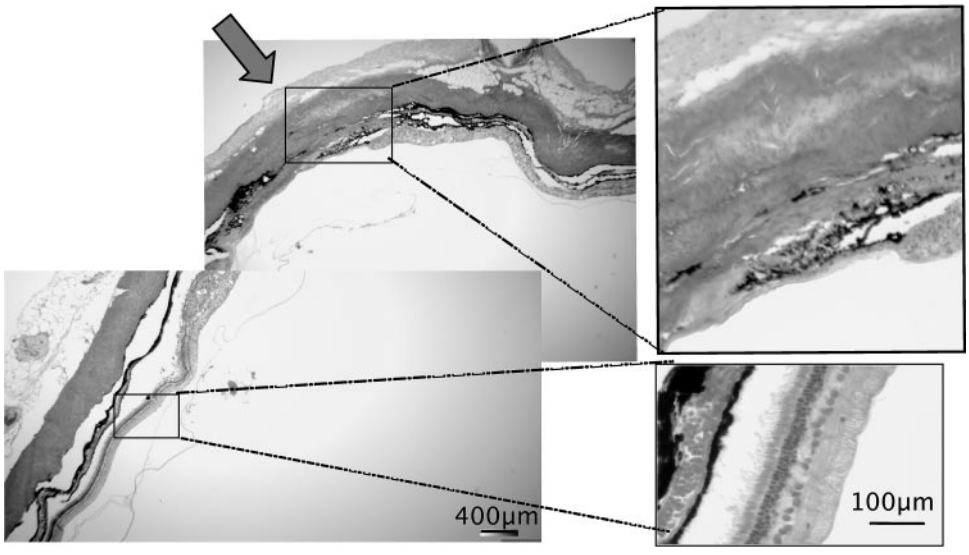

FIGURE 8. Microphotographs of an eye section from group 2, showing normal scleral thickness the site of implantation (*arrow*) and normal retina structure adjacent to it (*inset*; higher magnification).

(2) cumulated risk of rare but severe complications such as endophthalmitis, retinal tears, hemorrhages, and detachments; (3) cataract; (4) peak-and-valley drug levels, (5) toxic risk to ocular tissues when efficacy and toxicity thresholds are reached.[6,7] The development of biodegradable drug delivery systems to target the posterior segment of the eye, such as intraocular implants, may overcome most of these drawbacks since they can maintain stable long-term vitreous concentrations of drugs in the therapeutic range, reducing the frequency of intraocular injections and thus increasing the comfort for the patient, while reducing the observed complications.[1] Studies using biodegradable implants containing various agents have been reported[7–15] and dexamethasone biodegradable delivery systems have been developed for the prevention of inflammation after cataract surgery.[16–18] However, to date, no biodegradable polymeric drug delivery device is available for a release of active principle over more than 3 months.

Within the biodegradable polymers, the aliphatic polyester PCL, is of particular interest as it allows for a long-sustained and possibly modulated drug release rate.[19] PCL is a biodegradable and biocompatible semicrystalline polymer having a glass transition temperature of −60°C and melting point ranging between 59°C and 64°C, depending on its crystalline nature.[20,21] This polymer has a very slow degradation rate, making it suitable for long-term delivery extending over a period of more than 1 year. It is widely used in the pharmaceutical and biomedical fields as a biomaterial (e.g., suture, osteosynthetic material, artificial skin, or support of cellular regeneration) or in extended-release drug delivery systems targeting specific tissues within the body.[21] Because of its lack of toxicity and the great potential applications, PCL has already found wide use in various medical fields.[22]

PCL micro- or nanoparticles or solid implants have indeed been widely explored these past years for the administration of drugs by different routes and for the treatment of different diseases.[23–27] However, despite the potential of PCL, its utilization in ophthalmology, especially for delivery through the intraocular route has been poorly explored. For example, Beeley et al.[28] developed a subretinal drug delivery system made of PCL and containing triamcinolone acetonide as the drug. The developed device was implanted into the subretinal space of six rabbits, and no complications were observed during the 4-week follow-up period. The results of this work showed that PCL is well tolerated by the retinal tissue and that the implant can elute steroid for a period of at least 4 weeks without eliciting inflammatory response or complications.

According to Merkli et al.,[29] the PCL is characterized by a very low hydrolysis rate, which can vary from months to years. The in vivo release profile obtained from dexamethasone-loaded PCL implants showed that the drug was released slowly for 25 weeks, possibly controlled by diffusion through the channels and pores. Because of the hydrophobic nature of dexamethasone, its release in the vitreous is very slow. Then, a slight increase in dexamethasone vitreous concentration was observed at 41 weeks, which may be attributable to the bulk erosion of PCL. Overall, the release profile curve obtained showed long-term, well-controlled, stable release of dexamethasone in the vitreous with no significant peaks or valleys of drug release that could cause toxic reactions or no effect, respectively. The results showed that approximately 79% of dexamethasone was still present in the implants at 55 weeks, confirming the slow release of the drug and also the possibility of drug release for a period of 2 years.

The surface morphology of polymeric systems plays an important role in degradation and drug delivery.[30] The pores and channels in the matrices allow drug diffusion possibly not dependent on polymer degradation. PCL is a bioerodible polymer that undergoes type III erosion, which means that it leads to the formation of small, soluble molecules, by cleavage of the polymeric chains. PCL matrices degrade at low rates by hydrolysis of ester bonds and break down to their constituent monomer, the ε-hydroxycaproic acid that undergoes phagocytosis.[29]

The biodegradation study realized showed that PCL degrades slowly. The surface of the dexamethasone-loaded implants was initially smooth, with no evidence of pores or channels. After 1 month, the pores started to appear and were probably increased throughout the study. At the end of the follow-up, the number of pores and channels were highly increased, and the initial smooth surface had disappeared. Thus, water channels were formed during the degradation process, connecting the surface to the inner part of the implant and allowing drug diffusion throughout the water channels of the polymer matrix.[12] The pores and channels in the matrices may promote an increased water uptake by the implants, which may accelerate the degradation process. In PCL matrices, the observed pores can be attributed to the polymer degradation and to voids left behind by the release of the drug or to the absorption of water. The drug release profile observed was probably due to an initial release related to dexamethasone deposition on the surface followed by the release related to dissolution of the drug within the medium and diffusion through the channels and pores formed during polymer degradation.

Effective dexamethasone concentrations for suppressing various inflammatory processes range from 0.15 to 4.00 μg/mL.[31–35] The dexamethasone-loaded PCL implant developed therefore released the drug in the vitreous within this therapeutic range during 55 weeks. The in vitro release profile obtained from these implants showed that the device released the dexamethasone during at least 21 weeks within the therapeutic range, under sink conditions, which correspond to 25% of the total amount.[2]

During this period, no sign of decrease in drug release was observed, suggesting that the duration of the complete degradation of the implant inside the vitreous of the rabbits could reach 2 years. According to the in vivo profile, the drug release rate was faster than that observed in vitro, a fact that can be attributed to the environment surrounding the implant in the vitreous, which is not the same as the in vitro environment. Drug movement in the vitreous body and the elimination profile of the drug in the rabbit eye contribute to the faster drug release. The nature of the vitreous and surrounding tissue barriers creates concentration gradients within the vitreous that must be accounted for when developing ophthalmic drug therapy.[36,37]

Of note, the tolerance of the polymer was extremely good. Extrusion of two of the implants at the time of the suture degradation could be because the implants remained at the implantation sites, inducing forces on the eye wall. This phenomenon may not happen with smaller implants or implantation techniques that push the implants away from the implantation sites. No induced cataracts were observed in the control eyes or in those with dexamethasone-loaded polymers during the long-term follow-up, which could be explained by the low dose of dexamethasone that is released slowly from the implant. Most frequently, posterior segment diseases that are treated with long-term delivery of glucocorticoids require the maintenance of constant release of low doses of corticosteroids to keep the eye in a quiet state.

The first polymeric implant for dexamethasone release was made of PLGA (poly(D,L-lactic-*co*-glycolic acid); Posurdex; Allergan, Irvine, CA) and is able to release the drug for 6 weeks. In a clinical study, patients with persistent macular edema showed visual acuity improvement up to 90 days after implantation.[38] The PLGA implant was still present at 180 days, showing that an empty device may remain in the vitreous cavity, because of the well-known diffusion release profile of drug from PLGA.

Previous studies showed that PCL is well suited as a carrier of active agents provided the degradation products are not toxic and they can release the drug for a long period.[29] Such

biodegradable systems have several advantages over conventional systems for ophthalmic delivery and treatment of several disease could benefit from the release of therapeutic agents from these biodegradable systems.

Recently, one phase II clinical trial in which PCL was used as an implant for reconstruction of the orbit has been completed and the results were successful, showing that PCL is very well tolerated in human eyes.[39]

Our study shows that PCL is very well tolerated in rabbit eyes in the long-term, and is able to achieve a stable release of dexamethasone for at least 55 weeks. The size and the shape of the device that was used in this study cannot be applied directly to human eyes, but a miniaturized implant or microspheres made of PCL may have great potential for the sustained release of drugs in the vitreous. Still, because of the intrinsic properties of the polymer, such smaller drug delivery systems should have a much longer release profile than the available biodegradable intravitreous device.

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