Safety of Submacular Suprachoroidal Drug Administration via a Microcatheter: Retrospective Analysis of European Treatment Results

Manfred Tetz\(^a\)  Stanislao Rizzo\(^c\)  Albert J. Augustin\(^b\)

\(^a\)Berlin Eye Research Institute, Berlin, and \(^b\)Klinikum Karlsruhe, Karlsruhe, Germany; \(^c\)Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

Key Words
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Abstract
Purpose: To investigate the safety and feasibility of using a microcatheter for drug delivery in the suprachoroidal space in eyes with advanced, exudative, age-related macular degeneration (AMD) unresponsive to conventional therapy. Procedures: A unique microcatheter was used to deliver a drug combination consisting of bevacizumab and triamcinolone to the submacular suprachoroidal space. Twenty-one eyes of 21 patients with choroidal neovascularization (CNV) secondary to advanced, exudative AMD were followed over a 6-month postprocedure period. Results: The microcatheter was successfully and atraumatically inserted into the suprachoroidal space of all eyes. No serious intraoperative or postoperative complications including suprachoroidal hemorrhages were encountered. Postsurgically, complications consisted of 1 eye experiencing a transient elevation in intraocular pressure at 3 months, which was medically controlled, and 2 eyes (10.5%) with an apparent increase in nuclear sclerotic cataracts. Conclusions: Suprachoroidal drug administration was achieved without serious complication using a novel microcatheter. Direct drug delivery to the choroid can potentially increase local tissue drug levels and drug efficacy for the treatment of AMD and other diseases associated with CNV.

Introduction
Choroidal neovascularization (CNV), the process of submacular angiogenesis, is the principal cause of significant and permanent vision loss in patients with age-related macular degeneration (AMD) [1]. Despite the tremendous strides made in the treatment of CNV associated with a variety of chorioretinal disorders, some patients remain unresponsive to widely applied therapies including intravitreal injections of vascular endothelial growth factor antagonists [2, 3]. Limitations of intravitreal injections include the need for multiple injections [4] and the risk of complications such as endophthalmitis [5], retinal detachment [6] and cataract formation [7]. In addition, drug treatment of posterior segment diseases of the eye such as CNV may be hampered by poor intraocular penetration and rapid elimination of the drug from the eye [8].
The use of a microcatheter to access and deliver therapeutic agents to the suprachoroidal space for targeted treatment of posterior segment disease has been investigated in animals by Olsen et al. [9]. These authors observed that the administration of therapeutic agents to the suprachoroidal space to treat posterior segment disease may be desirable to allow for direct drug exposure to the choroid, potentially increasing local tissue drug levels and drug efficacy. This retrospective analysis of a noncomparative case series investigates the safety and feasibility of suprachoroidal microcatheterization and submacular drug delivery in humans.

Methods

Patient Selection

The research adhered to the tenets set forth in the Declaration of Helsinki. Each patient gave written informed consent after the nature of the procedure and options had been fully discussed. All patients were advised of the off-label nature of the treatment, lack of randomized clinical trial evidence of efficacy, and unknown potential for ocular and/or systemic side effects. Patients included in the analysis had to be at least 55 years of age with CNV secondary to advanced, exudative macular degeneration in the study eye. Patients who had been unresponsive to at least 3 prior treatments including thermal laser photocoagulation, verteporfin photodynamic therapy, or intravitreal injections of pegaptanib (Macugen™; Pfizer Inc., New York, N.Y., USA), bevacizumab (Avastin®; Genentech Inc., South San Francisco, Calif., USA) or ranibizumab (Lucentis®; Genentech Inc.) had been offered an alternative treatment trial with suprachoroidal administration of bevacizumab and triamcinolone acetonide. Vision in the study eye was 20/40 or worse Snellen equivalent using the Early Treatment Diabetic Retinopathy Study (ETDRS) test, and CNV had to extend beneath the geometric center of the foveal avascular zone.

Patients excluded from analysis were subjects who had CNV related to an ocular disease other than AMD (e.g. myopic degeneration or ocular histoplasmosis) or any coexisting ocular condition that could adversely impact vision assessments. Subjects were excluded if cataract surgery or refractive surgery occurred prior to completion of the 6-month follow-up visit. Subjects were also excluded if there had been difficulty in obtaining photographic or angiographic documentation of the CNV, prior intraocular surgery or any treatment for exudative AMD within 1 month of suprachoroidal treatment, a history of an abnormal elevation of intraocular pressure and to provide additional space for the administration of drugs to the suprachoroidal space [9]. The operational steps included priming the microcatheter with the bevacizumab injectate prior to insertion into the suprachoroidal space. A 1-ml syringe was attached to the microcatheter so that the microcatheter and syringe held a total of 4 mg of bevacizumab (0.16 ml). Upon placement of the microcatheter tip in the target location, the syringe contents were injected. The syringe was then exchanged for a 1-ml syringe containing 0.20 ml triamcinolone. The contents of the syringe were injected thereby delivering 4 mg of triamcinolone (0.10 ml) and leaving 0.10 ml in the dead space of the microcatheter. The total injectate volume was 0.26 ml.

Suprachoroidal access and administration of the injectate were performed in the operating room under monitored local anesthesia with intravenous sedation (Dormicum®; F. Hoffmann-La Roche AG, Basel, Switzerland). After induction of moderate sedation, ocular akesis and anesthesia were established with retrobulbar injection of local anesthetic. A full-thickness radial or limbal-parallel anterior scleral incision with a length of approximately 2–3 mm was created in the superotemporal quadrant. In some cases, a small amount of an ophthalmic viscosurgical device (e.g. Healon®; Abbott Medical Optics, Santa Ana, Calif., USA) was injected into the incision to allow the surgeon to visualize a clear path for insertion of the microcatheter into the suprachoroidal space and to separate the choroid from the sclera. An anterior chamber paracentesis was performed in some cases to lower the intraocular pressure and to provide additional space for the administered volume. The microcatheter was introduced into the suprachoroidal space through this incision and was advanced posteriorly. The position of the microcatheter was monitored through the operating microscope by visualizing the flashing, illuminated tip beneath the retina through a disposable vitrectomy.

Study Design and Methods

The study was a retrospective analysis of a noncomparative, interventional case series. The objective of this study was to evaluate the safety and feasibility of suprachoroidal drug delivery using a microcatheter in patients with advanced, refractory, exudative AMD. In addition, retrospective data analysis of the visual outcomes and clinical behaviors of the group was performed. Outcome measures included: best-corrected visual acuity (BCVA) using the ETDRS test; central subfield foveal thickness (CFT) and total macular volume by optical coherence tomography (OCT), and area of fluorescein leakage. Data analysis points were obtained at 1 day, 1 week, and then at 1, 3 and 6 months. Clinical assessments performed postoperatively included BCVA, biomicroscopy, tonometry, a dilated fundus examination, OCT and monitoring for adverse events. Fundus photography and fluorescein angiography were obtained when applicable.

Suprachoroidal Drug Administration

The procedure performed involved injections of bevacizumab in combination with triamcinolone acetonide (Triesence; Alcon Inc., Fort Worth, Tex., USA) administered via a microcatheter (iTRACK™400; iScience Interventional Corporation, Menlo Park, Calif., USA). The microcatheter was European Conformity (CE) marked and commercially available for fluid infusion and aspiration during ophthalmic surgery. It includes a flexible, small-diameter shaft with a 300-µm outer diameter, a 250-µm inner diameter, a fiberoptic in the lumen to provide a locating beacon near the tip and an atraumatic 400-µm distal tip designed for catheterization of ocular tissue spaces.

Patients had received a suprachoroidal injection of a combination of 4.0 mg triamcinolone with 4.0 mg bevacizumab. Determination of the dosage of triamcinolone and bevacizumab had been based on the dose and volume of drug used for intravitreal administration of bevacizumab or triamcinolone in other studies [7, 10–12] and previous investigations of the administration of drugs to the suprachoroidal space [9]. The operational steps included priming the microcatheter with the bevacizumab injectate prior to insertion into the suprachoroidal space. A 1-ml syringe was attached to the microcatheter so that the microcatheter and syringe held a total of 4 mg of bevacizumab (0.16 ml). Upon placement of the microcatheter tip in the target location, the syringe contents were injected. The syringe was then exchanged for a 1-ml syringe containing 0.20 ml triamcinolone. The contents of the syringe were injected thereby delivering 4 mg of triamcinolone (0.10 ml) and leaving 0.10 ml in the dead space of the microcatheter. The total injectate volume was 0.26 ml.

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lens placed on the eye (fig. 1). Once the position of the microcatheter tip beneath the macula was confirmed, the drug injectate was delivered through the microcatheter. The microcatheter was then removed, and the scleral and conjunctival incisions were closed with 8-0 vicryl sutures. No penetration into the vitreous cavity was performed either during surgery or with a sclerotomy.

Results

Twenty-one patients met the eligibility criteria and were evaluated. All patients were Caucasian with a mean age of 75.4 years (standard deviation or SD = 6.4; range 60–85 years). Nine patients were male and 12 were female. Fourteen patients (66.7%) had lesions characterized as occult CNV, 4 (19.0%) as predominantly classic, and 3 (14.3%) as minimally classic CNV; most lesions were very advanced. Prior to suprachoroidal drug administration, previous therapy included intravitreal injections of bevacizumab and/or ranibizumab in 18 patients. In addition to this injection therapy, 7 patients received pegaptanib and 4 patients underwent photodynamic therapy treatments; 1 subject had photodynamic therapy only. Of eyes receiving intravitreal injections, the average number of intravitreal injections per eye was greater than 3.

Use of the microcatheter was accomplished in all eyes. During suprachoroidal drug administration, a slight elevation of the retina had been observed through the surgical microscope in the area of the injection, which resolved within the first postoperative week. The drug injectate was not evident during follow-up examination. No intraoperative complications had been observed and, in particular, no suprachoroidal hemorrhage had occurred.

Nineteen eyes were phakic and 2 eyes were pseudophakic at the time of surgery. The average baseline BCVA was 0.98 logMAR (SD = 0.34), characteristic of advanced macular degeneration. At the 1-month follow-up visit, the mean BCVA was 0.92 logMAR (SD = 0.34); at 3 months the mean BCVA was 0.96 logMAR (SD = 0.33), and at 6 months it was 0.93 logMAR (SD = 0.4). A slight improvement in average BCVA at 1 and 6 months was observed, but no time point reached statistical significance compared to baseline values (p = 0.65, two-tailed paired t test at 6 months).

The preoperative CFT was 407.2 µm (SD = 229.8). Subsequent to suprachoroidal drug administration, the average CFT showed an initial decrease at 1 month to 333.3 µm (SD = 179.4), remaining stable at 3 months with an average CFT of 333.6 µm (SD = 170.3) and trending toward preoperative levels at 6 months (384.8 µm, SD = 265.7). Eleven of 18 eyes (61.1%) showed a decrease in CFT of at least 10% at 1 month postoperatively, 8 of 18 eyes (44.4%) at 3 months postoperatively, and 5 of 16 eyes (31.3%) at 6 months postoperatively.

Complications and Secondary Procedures

Of the 21 eyes in the study, 1 eye (4.8%) experienced an elevation of intraocular pressure above 21 mm Hg at the 3-month visit, returning to the preoperative level at 6 months following temporary glaucoma medication therapy. Of eyes which were phakic at baseline, 2 of 19 eyes (10.5%) experienced an apparent increase in nuclear sclerosis. One eye was reported to increase from grade 1 nuclear sclerosis at baseline to grade 2 at 1 month, and the second eye increased from grade 2 nuclear sclerosis at baseline to grade 3 at 3 months. No suprachoroidal hemorrhages were observed, and there was no visible evidence of retinal or choroidal tissue trauma that could be related to the procedure on any of the postoperative examinations or imaging studies. None of the patients required secondary procedures during the course of the 6-month follow-up period.

Case Report

A 75-year-old Caucasian female with subfoveal CNV secondary to advanced macular degeneration in the left eye (fig. 2a) had previously been unsuccessfully treated with 3-monthly injections of ranibizumab, most recently 10 months prior to baseline examination. Visual acuity was 20/320 tested at 1 m. Fluorescein angiography showed mottled early hyperfluorescence (fig. 2b) with a mild increase in the late frames (fig. 2c) consistent with occult CNV. OCT revealed extreme macular thickening (fig. 2d) with a subfield CFT measuring 760 µm. Horizontal (fig. 2e) and vertical...
Fig. 2. After 3 intravitreal injections of ranibizumab, 75-year-old Caucasian female prior to suprachoroidal medication delivery. Visual acuity is 20/320 at 1 m. a Fundus photograph showing macular edema, CNV and subretinal fibrosis. b, c Early (b) and late (c) fluorescein angiography frames consistent with occult CNV. d Macular thickening is visible on spectral OCT. e, f Horizontal (e) and vertical (f) OCT images showing large central outer retinal cysts and disruption of the retinal pigment epithelium (RPE) and photoreceptors.
Fig. 3. Same patient as in figure 2 at 1 month following suprachoroidal delivery of bevacizumab and triamcinolone. Visual acuity was unchanged. a Fundus photograph. b, c Early (b) and late (c) fluorescein angiography frames show a possible decrease in late leakage as compared to baseline. d OCT revealed a reduction in macular thickening. e, f OCT displays a complete resolution of the intraretinal cysts but with persistent mild juxtafoveal macular edema and photoreceptor disruption.
(fig. 2f) tomograms exhibited large central outer retinal cysts and disruption of the outer reflective bands corresponding to the retinal pigment epithelium (RPE), photoreceptor inner/outer segment boundary and external limiting membrane. The patient underwent suprachoroidal drug administration of bevacizumab and triamcinolone in the submacular region. Intraoperative elevation of the retina and RPE was visible during drug injection, but no intraoperative or postoperative tissue disruption or hemorrhage was observed. The suprachoroidal bleb was no longer visible 1 week later. One month after the procedure, visual acuity was unchanged. Fundus examination (fig. 3a) showed a reduction in macular thickening also confirmed on OCT (fig. 3d). Subfield CFT had decreased to 344 μm. Mottled hyperfluorescence was still present in both early (fig. 3b) and late (fig. 3c) angiography frames, although perhaps decreased from preoperative intensity. A complete resolution of the intraretinal cysts with reappearance of normal foveal contour, but persistent mild juxtafoveal macular edema, was noted on horizontal (fig. 3e) and vertical (fig. 3f) OCT images. However, substantial disruption of the RPE, photoreceptor inner/outer segment boundary and external limiting membrane still remained consistent with the finding of poor visual acuity and longstanding end-stage AMD. At 3 and 6 months, examination remained essentially unchanged although visual acuity had improved slightly to 20/250 at 1 m. No long-term complications or evidence of catheter placement were observed.

**Discussion**

The safety of targeted delivery of a drug injectate in the submacular suprachoroidal space with a microcatheter was investigated in humans. Similar catheters have been successfully used in the human eye for entering Schlemm’s canal in glaucoma surgery and for administering hyaluronic acid molecules for dilating the canal [13–15]. Olsen et al. [9] evaluated the pharmacokinetics of a posterior drug administration procedure by means of microcatheterization of the suprachoroidal space in the pig animal model. Catheterization was performed in 93 of 94 animals, and either 1.5 or 3.0 mg of triamcinolone acetonide were administered to the suprachoroidal space of the posterior pole. Histopathology demonstrated normal anatomy in uncomplicated cases. The drug demonstrated very high tissue concentration in the choroid with prolonged residence time up to study termination 4 months after administration. In addition, they found that the drug was measurable at very low levels in the systemic circulation. The choroid showed significantly higher levels of drug as compared to the retina by a factor of 10 at all time points. No sight-threatening adverse events associated with the drug or the use of the microcatheter were reported. Olsen characterized a relatively large anatomic space for suprachoroidal drug delivery and concluded that microcatheterization of this space can be performed in a safe and reproducible manner by using a careful surgical technique. Our study on a relatively small number of patients shows that microcatheterization can also be applied safely in human eyes. Serious complications related to the surgical technique were not observed.

One potential advantage of suprachoroidal drug administration as compared to intravitreal drug administration was that, during the observable period, only one surgical procedure was necessary to significantly reduce retinal swelling. Some loss of effect was noted between 3 and 6 months postoperatively. Repeated monthly injections were avoided, thus contributing to patient satisfaction and compliance. The effect was observed in eyes previously unresponsive to standard therapies. Even if the outcome was only comparable, costs related to repeated intravitreal injections may be reduced. Another potential benefit is that a higher concentration of the drug in the choroid can be achieved and, as observed by Olsen et al. [9] in the pig model, the persistence of the drug in the choroid may be prolonged while potentially minimizing systemic drug levels. Whether this leads to better functional results cannot be answered by this study.

The drug is administered directly to the posterior pole, thus potentially reducing but not completely avoiding side effects in the anterior segment of the globe such as glaucoma or cataract formation. The suprachoroidal space, which has focal, equatorial connections at the vortex ampullae, is limited anteriorly in the region of the scleral spur and posteriorly by the transscleral connections of the short posterior ciliary vessels to the choroid [16]. Therefore we hypothesize that the drug reaches the anterior segment in minor concentrations relative to intravitreal injections, possibly decreasing side effects.

Our study shows that the BCVA remained stable over a postoperative period of 6 months in eyes previously not responsive to standard therapies, indicating the feasibility of microcatheterization without major complications. A flexible microcatheter was able to access the submacular suprachoroidal space without resulting in suprachoroidal hemorrhage. After introducing the microcatheter through a careful scleral incision, the position of the device beneath the macula was monitored through a vitrectomy lens by observing the illuminated tip. Further studies on a larger number of patients comparing this technique to conventional intravitreal drug injections should be performed to determine the value and appropriate patient selection for microcatheter drug treatment. Other medications or drug concentrations currently not suitable for intravitreal injections due to pharmacokinetics may be evaluated in the future.
Submacular Suprachoroidal Drug Administration via a Microcatheter

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Disclosure Statement

Dr. Tetz is a consultant for iScience Interventional Corporation. Dr. Augustin and Dr. Rizzo have no proprietary interest.

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