Suprachoroidal Drug Delivery – A New Approach for the Treatment of Severe Macular Diseases

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Abstract
In this article, we review recent research in suprachoroidal drug administration for the treatment of advanced, refractory, retinal disease. A microcatheter (iTRACK™ 400) has been used to access and deliver drugs to the suprachoroidal space. This technology has been investigated in several animal models as well as in patients with advanced disease stages and/or who are unresponsive to conventional treatments. In groups with either age-related macular degeneration (AMD) and/or macular oedema resulting from other diseases, significant effects were achieved by using this technology to apply steroids and/or anti-vascular endothelial growth factor (VEGF) drugs, with no surgical or postoperative complications observed. Suprachoroidal drug administration directly adjacent to the choroid in the submacular region might therefore be a potential treatment for many retinal diseases. Human pilot studies in patients with advanced, refractory retinal disease that is unresponsive to conventional treatments showed some increase in residual vision and significant reduction of macular oedema, with few complications. Prospective trials are necessary to confirm the pilot results obtained by different research groups.

Keywords
Age-related macular degeneration, exudates, macular oedema, microcatheter, suprachoroidal space

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Intravitreal drugs are currently approved for the treatment of both age-related macular degeneration (AMD) and macular oedema resulting from diabetes or vein occlusion. However, the major drawback of these drugs and/or an intravitreal monotherapy strategy is the need for repeated injections, with most of the drugs requiring injections on a monthly to bimonthly basis. In addition, some of the disease stages do not respond adequately to treatment. Thus, there is currently a medical need for new innovative technologies that reduce the requirement for repeated injections and optimise treatment safety. Moreover, to reduce the risk of adverse effects, exposure of the anterior segment should be limited, which can be achieved by a suprachoroidal approach.

In a rabbit model using dynamic contrast-enhanced magnetic resonance imaging, it has been shown that intrascleral catheter infusions expand the suprachoroidal layer. The model drug, gadolinium-diethylenetriaminopentaacetic acid, was rapidly delivered to the macula with limited anterior segment exposure. However, several other approaches to get the drug nearer to the target without diminishing safety did not show convincing results.

Finally, using a porcine model, Olsen and co-workers demonstrated that the suprachoroidal space might be the ideal reservoir for sustained-release formulations. Here, a steep concentration gradient can be established for drug diffusion to the target. The authors directly accessed the posterior segment through the suprachoroidal space by using either a rigid or flexible cannula. Interestingly, by positioning a triamcinolone acetonide depot into the suprachoroidal space, pharmacokinetic studies showed local drug concentrations in both the choroid and retina that were high enough to exert positive effects. In addition, the drug stayed in place for up to four months and an excellent safety profile was also demonstrated. Thus, suprachoroidal administration or targeted delivery of drugs directly to the suprachoroidal space might be of combined clinical benefit.

Method
The use of a microcatheter (iTRACK™ 400) to access and deliver drugs to the suprachoroidal space was first investigated in a porcine model by Olsen et al.1 These authors evaluated posterior drug administration by catheterising the suprachoroidal space in 93 out of 94 pigs. Triamcinolone acetonide was injected into the suprachoroidal space to characterise the pharmacokinetics and pharmacodistribution of steroid administration. Fluorescein angiography, fundus examination and histopathology were performed to investigate the safety of the procedure.

Subsequent to publication of the work by Olsen et al., patients with advanced, refractory AMD were treated in a pilot study by Chang and co-workers (Chang et al., oral presentation summarised in Augustin and Rizzo). In the study, patients were selected who had choroidal...
neovascularisation (CNV) secondary to advanced, exudative AMD and who were either not candidates for conventional treatments or had failed multiple therapies. A microcatheter was introduced into the suprachoroidal space through a port created in the pars plana and advanced posteriorly by visualising the illuminated tip beneath the retina through a BIOM lens. An endoilluminator was placed in the vitreous cavity through a 25-gauge sclerostomy port to aid visualisation. Bevacizumab (Avastin®) and/or triamcinolone was injected into the submacular suprachoroidal space. Over a six-month follow-up period, patients were examined with fundus photography, fluorescein angiography (FA) and optical coherence tomography (OCT) to document their retinal appearance and function.

After the presentation of the work by Chang et al., other groups investigated the suprachoroidal administration of a combination of bevacizumab and triamcinolone to the submacular suprachoroidal space in eyes with CNV secondary to advanced, exudative AMD that failed to respond to conventional therapy.1 A microcatheter was introduced into the suprachoroidal space through a small scleral incision in the supertemporal quadrant and was advanced posteriorly. The tip of the microcatheter was guided through the operating microscope with a disposable vitrectomy lens. No sclerostomy port or other access to the vitreous cavity was used.

Over a six-month follow-up, patients were examined with fundus photography, FA and OCT.

Recently, another pilot study by Rizzo and co-workers included eyes with retinal vein occlusion or diffuse diabetic macular oedema accompanied by massive subfoveal hard exudates (SHE) that was unresponsive to multiple intravitreal injections. The eyes underwent a single treatment in which a combination of bevacizumab and triamcinolone was administered to the submacular suprachoroidal space via a microcatheter. The surgical method followed the method described above. The patient follow-up included best corrected visual acuity (BCVA), vascular leakage, macular thickness, extent of hard exudates and the incidence of adverse events.

**Result of the Pilot Evaluations and Further Comments**

In the animal study by Olsen et al., histopathology demonstrated normal anatomy in uncomplicated cases. The injectate, triamcinolone acetonide, remained in the local ocular tissue for at least 120 days. The choroid showed significantly higher levels of drug compared with the retina by a factor of 10 at all time points. The drug was also detected for a significantly longer period of time in ocular tissues when administered in the suprachoroidal space compared with the same dose administered by intravitreal injection. No adverse response associated with the drug or the use of the microcatheter was observed.

In the AMD pilot study by Chang and co-workers, the average preoperative BCVA was 1.78 ± 0.41 logMAR units, which increased to 1.40 ± 0.60 at three months and was 1.63 ± 0.71 at 12 months. Overall, BCVA showed a trend towards improvement, but did not reach statistical significance. After three months, the visual acuity appeared to regress towards preoperative levels. The average central subfield foveal thickness (CFT) appeared to diminish after surgery at all time points. Total macular volume significantly decreased from baseline levels at six months. Only two eyes had an elevation of intraocular pressure (IOP) above 21 mmHg at any postoperative visit beyond one week, both eyes reaching an IOP of 24 mmHg and resolving without treatment. Of the six eyes that were phakic at baseline, one eye with a pre-existing grade 2+ nuclear sclerotic cataract developed a 1+ posterior subcapsular cataract during the follow-up period.4

In the AMD pilot study by Tetz and co-workers, a slight improvement in the average BCVA at one month and six months was observed, but no time point reached statistical significance compared with baseline. Preoperative CFT was 407.2 μm (SD=229.8), decreasing at one month to 333.3 μm (SD=179.4), remaining stable at three months and trending towards preoperative levels at six months (384.8 μm, SD=265.7). No serious intra- or postoperative complications, including suprachoroidal haemorrhages, were encountered. Postsurgically, complications consisted of one eye experiencing a transient elevation in IOP at three months, which was medically controlled, and two eyes with an observed increase in nuclear sclerotic cataracts.5

In the pilot study by Rizzo et al., patients were suffering from central retinal vein occlusion, branch retinal vein occlusion, and chronic diabetic macular oedema. BCVA improved by two lines or more in three eyes and remained stable in three eyes for the duration of the study. At one or two months post-procedure, the macular hard exudates underlying the fovea were almost completely resolved in all
eyes and macular oedema was significantly reduced (see Figures 1 and 2). No surgical or postoperative complications were observed.

Discussion and Conclusions

The catheter technology we report on in this paper is already successfully in use in the human eye for entering Schlemm’s canal in glaucoma surgery and for administering hyaluronic acid molecules for dilating the canal. The targeted delivery of drugs into the suprachoroidal space with a microcatheter was investigated by various studies in animals and humans. Histopathology demonstrated normal anatomy in uncomplicated cases. The drug demonstrated a very high tissue concentration in the choroid with prolonged residence time. In addition, only very low drug levels were detected in the systemic circulation. The choroid showed significantly higher levels of drug compared with 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 characterised a relatively large anatomic space for suprachoroidal drug delivery and concluded that microcathectisation of this space can be performed in a safe and reproducible manner by using careful surgical technique. The drug is administered directly to the posterior pole, thus potentially reducing but not completely avoiding adverse effects in the anterior segment of the globe, such as glaucoma or cataract formation. Anatomically, the suprachoroidal space as a drug reservoir is ideal to reduce anterior segment adverse effects.

A further advantage of the suprachoroidal drug administration approach is its minor invasive non-intravitreal surgical procedure combined with significant effects over a long period of time, which is between three and six months for AMD and possibly longer for macular oedema and exudate treatments. Moreover, the effect was observed in eyes previously unresponsive to standard therapies.

The study by Tetz and co-workers nicely shows that the BCVA remained stable over a postoperative period of six months in eyes previously not responsive to standard therapies, thus indicating the feasibility of microcathectisation without major complications. The authors state that further studies on a larger number of patients might be a useful option as it enables direct exposure of the choroid and in reducing macular thickness in retinal vasculopathies. Administering therapeutic agents through the suprachoroidal space might be a useful option as it allows direct exposure of the choroid to the drug, potentially increasing choroidal drug levels. However, larger clinical prospective trials are necessary to elucidate whether this is a useful approach in the clinical routine for the patient groups mentioned here.

There might be other uses for the suprachoroidal approach in addition to the treatment of AMD. The treatment of subretinal plaque-like exudations resulting from diabetic retinopathy or vein occlusions, as well as oedematous that are not responding to any conventional treatment, remain a major challenge. In those eyes not responding to conventional drug injections, aggressive treatments, including vitrectomy and lavege techniques, have been performed with encouraging short-term, but unsatisfactory long-term, results.

The unfavourable prognosis in eyes with subfoveal hard exudates after a natural course or surgical approaches, including pars plana vitrectomy and retinotomy plus lavege, encouraged Rizzo and co-workers to develop alternative treatment options. In their study, the rationale for delivering a high concentration of anti-vascular endothelial growth factor (VEGF) directly to the macula through the suprachoroidal space was clearly supported by the rapid reabsorption of the refractory massive exudates that did not respond to other treatments. The exudates diminished or resolved in all eyes after one month and macular oedema was reduced. This effect on macular oedema was also observed in macular oedema resulting from vein occlusion that did not respond to other treatment. No intra- or postoperative complications occurred. This study was a preliminary non-comparative case series in which only a few patients were investigated. Interestingly, the patients also demonstrated a good physiological response to suprachoroidal infusion of anti-VEGF based on their visual acuity. After the absorption of the exudates, functional improvements were observed within one to two months of treatment and the outcomes achieved lasted for the duration of the follow-up period. The authors speculated that the effectiveness of the procedure resulted from the direct delivery of the drug to the target.

The results of this study suggest that the suprachoroidal application of bevacizumab and triamcinolone acetonide to the submacular region is beneficial in both reabsorbing massive hard exudates and in reducing macular thickness in retinal vasculopathies. Administering therapeutic agents through the suprachoroidal space might be a useful option as it enables direct exposure of the choroid to the drug, potentially increasing choroidal drug levels. However, larger clinical prospective trials are necessary to elucidate whether this is a useful approach in the clinical routine for the patient groups mentioned here.