

SURGICAL DRUG DELIVERY ROUNDUP

These novel innovations have helped clinicians improve therapeutic access to the posterior pole.

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Ophthalmic drugs can be delivered by multiple pathways, including systemic, topical, periocular, subconjunctival,

sub-Tenon's, suprachoroidal, intracameral, intravitreal, and subretinal. Intravitreal injections—commonly of anti-VEGF agents but also corticosteroids, antibiotics, antivirals, antifungals, complement inhibitors, and chemotherapy—were the most performed ophthalmic procedure among the Medicare Fee-For-Service population in 2020, based on the authors' analysis of the publicly available Part B National Summary Data File. In-clinic suprachoroidal injections may become more common with the development of the suprachoroidal microinjector (SCS Microinjector, Clearside Biomedical) and the FDA approval of suprachoroidal triamcinolone acetonide (Xipere, Bausch + Lomb and Clearside Biomedical).^{1,2}

Certain treatments, however, are best administered surgically, including intravitreal devices for sustained release, subretinal tissue plasminogen activator injection for submacular hemorrhage displacement, and subretinal gene therapy. More generally, options for surgical drug delivery include intravitreal implants and subretinal access by vitrectomy and retinotomy or a suprachoroidal approach.

IMPLANTED INTRAVITREAL DEVICES

Intravitreal implants elute small concentrations of medication over long periods and are an attractive option to reduce treatment burden associated with neovascular retinal diseases such as wet AMD and diabetic macular edema. Examples of this technique include the fluocinolone acetonide intravitreal implant (Retisert, Bausch + Lomb),³ the NT-501 encapsulated cell therapy implant (Neurotech Pharmaceuticals),⁴ and the port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche).⁵

The PDS is implanted in the OR, and refill-exchanges are performed in the clinic. Although the company voluntarily recalled the PDS,⁶ the surgical technique is described here

because a similar approach may be used in the future. To implant this device, place an infusion line in the inferotemporal quadrant, followed by a superotemporal corneal traction suture. Perform a conjunctival peritomy in the superotemporal quadrant to expose bare sclera, followed by a 3.5 mm scleral cutdown incision that is parallel and 4 mm posterior to the limbus. Next, ablate the choroidal pars plana vasculature using a 532 nm laser endoprobe. Incise the pars plana using a 3.2 mm blade, and achieve hemostasis using fine-tip diathermy. Insert the implant, close the conjunctiva and Tenon's capsule, and remove the infusion line.⁷

The voluntary recall did not include the refill-exchange solution or needle. Thus, patients who received the implant can continue receiving in-office refill-exchange procedures.

SUBRETINAL ACCESS BY VITRECTOMY

Subretinal drug delivery offers the advantage of placing the medication in direct contact with the target (eg, placing tissue plasminogen activator in contact with blood for a subretinal hemorrhage or placing a viral vector in contact with the photoreceptors and retinal pigment epithelium [RPE] for gene therapy).⁸ In the case of viral vectors for gene therapy, subretinal administration also results in reduced inflammation compared with intravitreal injection due to the immune-privileged nature of the subretinal space.⁹ Voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics)

AT A GLANCE

- ▶ Intravitreal implants elute small concentrations of medication and may reduce treatment burden.
- ▶ Subretinal drug delivery places the medication in direct contact with the target.
- ▶ The subretinal space can be accessed suprachoroidally, which avoids a vitrectomy and retinotomy.

is the first FDA-approved therapy using this technique; however, many trials are underway for other gene therapies delivered via subretinal surgery.¹⁰

Begin subretinal delivery with a core vitrectomy, induce a posterior vitreous detachment, and create a retinotomy. Either directly inject the vector into the subretinal space, creating a bleb via a subretinal cannula and pneumatic injector (Figure), or administer the vector after creating a saline pre-bleb, which may minimize drug reflux. Intraoperative OCT can help to confirm subretinal administration. Adjunctive techniques such as subretinal air or fluid-air exchange can be considered, although these are not always necessary. In some protocols, the patient is placed in a supine position postoperatively to ensure the bleb remains in the posterior pole.

Disadvantages of this technique include the need for a vitrectomy (due to its associated risks) and a retinotomy, with the resulting possibility of medication reflux leading to dose reduction or epiretinal membrane formation, damage from transient neurosensory retinal detachment, and macular hole formation. Inadvertently inserting the subretinal cannula too deep can lead to RPE damage or suprachoroidal infusion, whereas shallow insertion can lead to retinoschisis.

SUBRETINAL ACCESS VIA SUPRACHOROIDAL CATHETER

The subretinal space can also be accessed surgically via a suprachoroidal approach using a tunneled catheter with a microneedle that penetrates the choroid and RPE. This surgical modality has entered human clinical trials for suprachoroidal-to-subretinal delivery of gene and cell therapies.

The general surgical technique involves first accessing the suprachoroidal space by a localized conjunctival peritomy and scleral cutdown, then introducing and tunneling a catheter under direct visualization and chandelier illumination. Once in the desired location, the needle is deployed to the subretinal space and the medication is delivered.¹¹

This approach has been used to treat geographic atrophy with GT005 (Novartis) using the Orbit Subretinal Delivery System (Gyroscope Therapeutics), palucorcel (Janssen Pharmaceuticals),¹² and OpRegen (Lineage Cell Therapeutics).¹³ The scientific programs for GT005 and palucorcel have since been discontinued.

An advantage of this approach is the avoidance of vitrectomy and its associated complications. This can be especially helpful for gene therapies that may be given to younger patients with a more adherent hyaloid. Furthermore, this technique obviates the need for a retinotomy, preserving retinal tissue and avoiding reflux of medication into the vitreous chamber via the retinotomy site.

THE FUTURE

We have made significant advances in surgical drug delivery to the posterior segment, typically in tandem with new drug

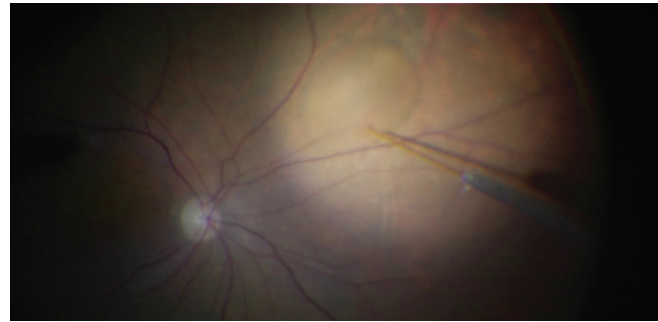


Figure. Subretinal bleb creation for the administration of RGX-314 (Regenxbio) gene therapy.

developments. Our toolkit continues to expand, and these exciting developments may provide new options for patients, ultimately changing the field for the better. ■

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