

Achieving Drug Delivery Via the Suprachoroidal Space

Use of the suprachoroidal space for drug delivery may achieve sustained delivery of therapeutics close to the source of retinal or choroidal pathology.

BY DEBRA A. GOLDSTEIN, MD

Macular edema is a feature of many conditions, including but not limited to uveitis, retinal vein occlusion, age-related macular degeneration, and diabetic macular edema. The anatomic and sight-threatening consequences of swelling of the macula are well known.¹ Ideally, therapeutic agents intended to counteract edema would be delivered as close to the underlying pathology as possible so as to achieve a rapid response, and they would have a sustained effect that would reduce the need for readministration.

Several mechanisms have been proposed to achieve local availability of antiinflammatory agents at the source of retinal and/or choroidal pathology. Classically, this has been achieved by either intravitreal or periocular injection. These approaches, however, require frequent injections to achieve a continued therapeutic dose, and, thus, exposure to potentially subtherapeutic doses during the treatment intervals—in addition to the increased risk of injection-related complications such as retinal tear, vitreous hemorrhage, retinal detachment and endophthalmitis. Recently, sustained-release implants, which ensure a more consistent and constant delivery of drug at therapeutic levels, have been approved by the US Food and Drug Administration. These implants, injected or sutured into the vitreous cavity, are potentially very effective but still carry the risks associated with their placement inside the eye.

A novel approach currently in development is the use of the suprachoroidal space between the sclera and choroid as a reservoir for ophthalmic therapeutic agents. Clearside Biomedical has developed proprietary microneedles for delivery of drug to this space. The company's preclinical testing indicates that the suprachoroidal space can hold up to 200 μ L of fluid, suggesting that this space can be used for the sustained delivery of a drug close to the source of pathology

via a single injection. There may be additional advantages to this route of ocular drug delivery.

SUPRACHOROIDAL DRUG DELIVERY OF CORTICOSTEROIDS

Current options for the local use of triamcinolone acetonide include intravitreal injection and periocular injection. Each method has its own advantages and disadvantages. Studies indicate that intravitreal injections may have superior efficacy compared with periocular injections.^{2,3} Intravitreal injections also impart higher levels of a drug to the vitreous than periocular injection, which may accelerate the therapeutic effect.⁴ Intravitreal injections, however, confer risks of endophthalmitis, retinal tear and detachment, and vitreous hemorrhage. As well, patients may develop visually disturbing floaters.

It has been suggested that periocular injections might have a longer duration of effect than intravitreal injections. In addition, sub-Tenon injections of triamcinolone may be safer, but they may not be as effective as intravitreal triamcinolone for the treatment of macular edema.^{2,3}

Injection into the suprachoroidal space may offer the best of both worlds. Creating a depot of drug under the sclera instead of within the vitreous cavity avoids the risk of vitreous hemorrhage, retinal detachment, and floaters, while concentrating drug where it is most needed. Animal data support this hypothesis. Triamcinolone acetonide injection into the suprachoroidal space was compared with intravitreal triamcinolone injection in a porcine model of posterior uveitis.⁵ In the study, 0.2- and 2.0-mg suprachoroidal triamcinolone injections were as effective in reducing ocular inflammation as a 2.0-mg intravitreal injection; however, a 0.2-mg intravitreal injection of triamcinolone was not effective in this model. These data suggest that a lower dose of

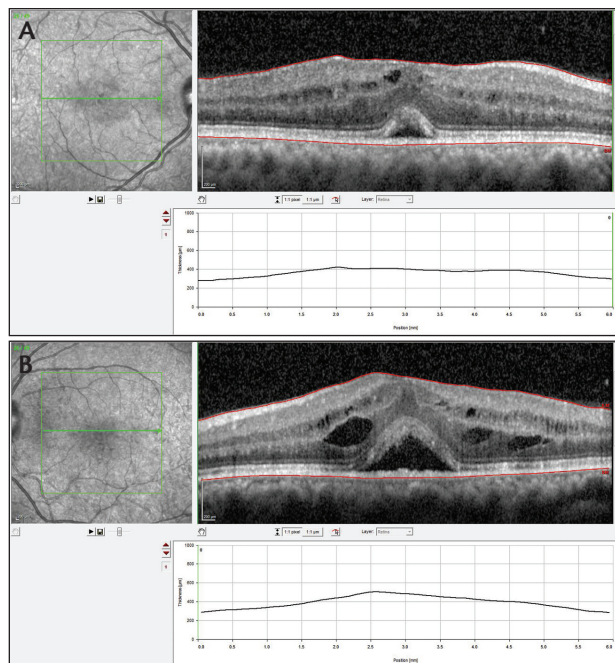


Figure 1. A 52-year-old woman with bilateral chronic uveitis and cystoid macular edema. Small foveal detachments can be seen in the right (A) and left (B) eye.

triamcinolone may be used if the agent is delivered suprachoroidally versus intravitreally, allowing the potential for a reduction in dose-dependent side effects.

Injection into the suprachoroidal space may also increase the duration of a drug's effect. Animal studies of triamcinolone acetonide injected into the suprachoroidal space of monkey and pig eyes have demonstrated that the drug remains in local ocular tissues for at least 120 days.⁶

The dose delivered can be titrated by varying the concentration of drug itself and/or the volume delivered via the microneedle. How this might affect duration of action, however, remains to be studied in humans.

EARLY EXPERIENCE

I am involved in a small phase 1 clinical trial evaluating the suprachoroidal delivery of steroids to patients with cystoid macular edema secondary to noninfectious uveitis. Data from this study should supply more evidence about the duration of efficacy when the suprachoroidal space is used as a reservoir.

I have injected 4 patients as part of the phase 1 trial and have found the injection procedure itself to be similar to that of an intravitreal approach. It has not been difficult to target the suprachoroidal space. The needle and delivery system have been redesigned since the start of the trial, making the needle thinner and sharper, and thus very easy to use. The phase 1 trial was performed with the investiga-

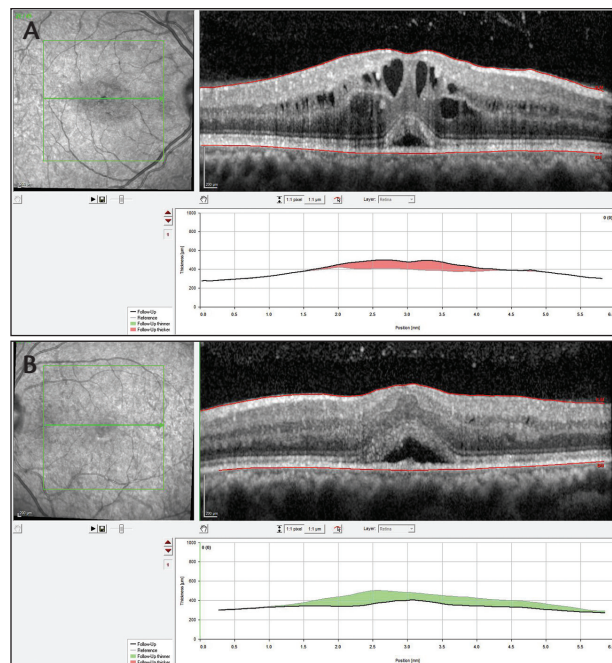


Figure 2. The same patient 1 week after receiving a sub-Tenon injection of triamcinolone in her right eye (A) and a suprachoroidal injection of triamcinolone in her left eye (B). Note that the left eye displays improvement of the macular edema, while the right eye appears slightly worse than at initial presentation.

tor having a choice of 900 or 1100 μm needle length, with the decision on needle size determined based on ultrasound measurement of scleral thickness. A proprietary adjustable length needle is in development. Although it is far too early to speculate about where suprachoroidal drug delivery may fit into the treatment paradigm for uveitis, the injection is easy to perform in the clinic setting and has, in my patients, been very effective (Figures 1 and 2). The injection is, however, more painful than intravitreal injection, presumably because of distension caused by the volume of drug injected. This will be addressed in the phase 2 trials by using a lower volume of injection.

OTHER APPLICATIONS

This review of the potential for drug delivery into the suprachoroidal space has focused on the delivery of corticosteroids for the treatment of macular edema. Several preclinical and animal studies suggest the feasibility of using this space for other applications. A study in a porcine model indicated that delivery of bevacizumab (Avastin, Genentech) to the suprachoroidal space resulted in more rapid decline in tissue levels compared with intravitreal injections, leading investigators to speculate that perhaps sustained-release

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formulations of larger molecule biologics might be necessary before this space becomes relevant.⁷ However, the study also noted that, while intravitreal injection delivered the drug preferentially to the inner retina, delivery via the suprachoroidal space occurred primarily at the level of the choroid, retinal pigment epithelium, and photoreceptor outer segments—anatomic regions that are more relevant to the pathophysiology of age-related macular degeneration.

Suprachoroidal drug delivery has also been studied for delivery of nanoparticle and microparticle suspensions,⁸ and studies have also looked at the potential to use the suprachoroidal space as a reservoir for sustained-release drug-eluting implants.⁹ Touchard and colleagues looked at the viability of using a technique called *suprachoroidal electrotransfer* to accomplish delivery of gene therapy via a nonviral route; this route appeared to avoid retinal complications associated with viral delivery of gene therapy, while still inducing a biologic response.¹⁰

CONCLUSION

Delivery of drug to the suprachoroidal space may provide therapeutic effect close to the source of retinal and choroidal pathology, which may in turn have an impact on the dose required to achieve a benefit, as well as on the duration of effect. These features are likely to provide distinct clinical advantages. It is important to note, however, that much of the data on suprachoroidal drug delivery at this point is in animal and preclinical models. We await the results of the phase 1 trial in humans to see if the potential of this mechanism for drug delivery is safe and worthy of future research. ■

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