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Revolutionizing Drug Delivery: Unveiling The Potential of Suprachoroidal Injection For Targeted Therapy

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ABSTRACT

The intricate structures of the eye's posterior segment pose significant challenges for effective drug delivery in the treatment of various diseases. Current modalities, such as topical and intraocular medications, often face barriers that limit their penetration, residence time, and bioavailability. This necessitates frequent dosing, impacting patient compliance and quality of life. Suprachoroidal injection emerges as a novel and promising approach for targeted drug delivery to the posterior segment. The suprachoroidal space, situated between the sclera and choroid, provides a minimally invasive route for medication delivery, offering advantages like higher drug concentrations, increased bioavailability, and prolonged action. This method also mitigates the risk of adverse events associated with other routes, particularly corticosteroid-related complications. This review discusses the potential of suprachoroidal injection, highlighting its benefits in overcoming anatomical barriers and improving therapeutic outcomes. However, further research is crucial to address existing challenges, including technological advancements, injection techniques, and considerations of cost and accessibility. Exploring synergies with biotech products, gene therapies, and cell-based treatments can pave the way for personalized and effective strategies in managing posterior segment eye diseases.

Keywords: Suprachoroidal injection, Controlled drug release, Retina, Posterior segment diseases, Ocular drug bioavailability, Ocular diseases

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INTRODUCTION

The landscape of ocular drug delivery is in constant evolution, presenting new challenges and opportunities in the field of ophthalmology. Treating posterior segment and retinal diseases is particularly challenging due to the eye's complex structures that act as barriers to drug delivery and bioavailability (1). Traditional administration methods, such as eye drops, periocular and intravitreal (IV) injections, and systemic medications, often require frequent dosing and can result in substantial side effects with long-term use(2). Recently, suprachoroidal (SC) injection has emerged as a novel strategy for targeted drug delivery to the posterior segment of the eye, offering an innovative approach to address these challenges (3).

The posterior segment of the eye consists of all the structures behind the anterior hyaloid membrane, including the vitreous, retina, choroid and optic nerve(4). The most common diseases of the posterior segment structures are age-related macular degeneration (AMD), diabetic retinopathy, diabetic macular edema, retinal vascular occlusions and noninfectious uveitis, and they are major contributors of visual impairment and blindness (5) Current pharmacologic treatments include mainly anti-vascular endothelial growth factor (VEGF) and corticosteroids administered via intravitreal (IVT) injections which have become the first-line treatment for many retinal diseases (6).

The suprachoroidal space (SCS), an anatomical niche nestled between the sclera and the choroid, provides a minimally invasive conduit for precise medication delivery. This approach not only enhances drug concentrations in the posterior segment, increasing drug bioavailability and duration of action but also minimizes the risk of corticosteroid-related adverse events through compartmentalization (7). the suprachoroidal space (SCS) as a route of drug administration to the posterior segment of the eye. As this avenue of drug delivery is continuously evolving, our review provides comprehensive and up to date information regarding its use for treating retinal diseases.

This review offers a comprehensive overview of SC injection, covering its rationale, techniques, biomechanics, and implications in treating diverse ocular diseases, particularly those affecting the posterior segment. We also explore the current challenges and future prospects of this technique.

We explore not only the application of this technique in clinical settings but also delve into preclinical studies for other ocular conditions such as glaucoma, retinitis pigmentosa, and various chorioretinal diseases. This review goes beyond simply informing clinicians about existing indications as we shed light on new therapeutic possibilities emerging from preclinical studies yet to be applied to human subjects. Furthermore, our examination of the biomechanics of SC injection serves to bridge the gap between theoretical understanding and clinical practice by

exploring how alterations in various physical parameters of the injection can influence its applicability.

To achieve this, we performed an extensive literature review, to ensure the inclusion of the latest advancements and insights. Through this exploration, we aspire to capture the current state of this technique, elucidate potential avenues for improvement and innovation, and provide a reference point for further research and clinical applications in this rapidly evolving field.

An Unmet Need

An ideal therapy is one that targets the exact area of pathology it is intended to treat, is easy to administer (requires little skill and can be performed as an office profile).

Current routes of drug delivery for therapeutics for conditions related to the posterior segment of the eye include topical, subtenon, subretinal and IVT injections. Each type of administration carries its own advantages and disadvantages. Topical administration is the least invasive but is often ineffective due to poor penetrance and low therapeutic levels at the posterior segment structure (scedure), achieves a long-lasting effect and has a good safety profile(8). Subretinal injections are very targeted, yet require an invasive surgical procedure, that also carries significant risks (9). IVT injection is easy to administer and can be performed in an office setting; however, it does not target a specific area and has adverse effects, including endophthalmitis, elevated intraocular pressure (IOP) and cataract progression (10)

ANATOMY AND PHYSIOLOGY

Choroid

The choroid, a layer in the eye, is nourished by blood from the posterior ciliary arteries as shown in figure 1. This blood flows through two key sub-layers of choroidal vessels, the Haller and Sattler layers, to reach the choriocapillaris, where arterial pressure reduces to a lower level. The choroid's thickness varies across its expanse, being thickest in the central macular region and thinnest at the oraserrata. Typically, in most 50-year-olds, the choroid measures about 287 μm subfoveally, though thickness can vary with age and ocular disease conditions (11).

The choroid plays a crucial role in supplying nutrients, particularly oxygen, to the retina, one of the body's most metabolically active tissues (Figure 1). Approximately 90% of the oxygen consumed by the outer retina, housing photoreceptors, and retinal pigment epithelium (RPE), is provided by choroidal circulation. Furthermore, the choroid features the highest blood flow rate of any tissue in the body. Despite the high metabolic demand of these tissues, the exiting venous blood maintains high oxygen tension, reflecting the choroid's efficient function in nutrient delivery and metabolic waste removal (12)

Located in the posterior pole, the choriocapillaries feature an intricate capillary network that is more irregular toward the periphery. The choroid's composition also includes loose connective tissue, fibroblasts, and melanocytes. In the post-choriocapillaris, blood is gathered in venules, followed by larger channels, to drain into the superior and inferior ophthalmic veins through the vortex veins (12).

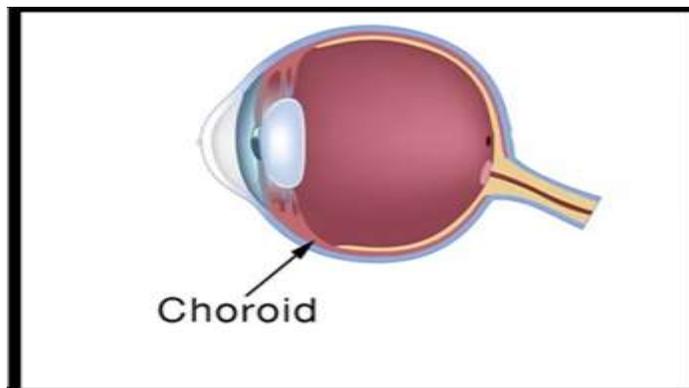


Figure 1: Anatomy of the Choroid.

Sclera

The sclera consists of collagen and a small number of elastic fibers embedded in a proteoglycan matrix. Its thickness varies, being the thinnest near the muscle insertion sites and thicker posterior to the limbus, where it terminates (13)

An essential characteristic of the sclera is its permeability, facilitating bidirectional molecular transport. Its permeability enables drug delivery via injections into the sub Tenon space. However, the sclera's hydrophilic nature means that its permeability to hydrophobic or amphiphilic substances, including certain medications, can vary. This property is a crucial factor to consider when planning periocular injections of pharmacological agents (14).

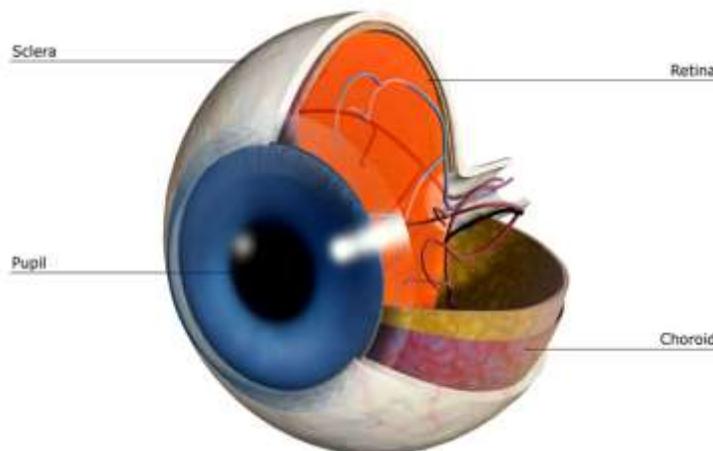


Figure 2: Anatomy of sclera

The thickness of the human sclera varies between individuals and across different regions of the eye. A histomorphometric study conducted by Vurgese, Panda-Jonas, and Jonas on 238 human eyes found that in non-axially elongated eyes (axial length ≤ 26 mm, with the average axial length usually being around 23 mm), the sclera was thickest at the posterior pole (0.94 ± 0.18 mm), followed by the peri-optic nerve region (0.86 ± 0.21 mm), and the midpoint between the posterior pole and equator (0.65 ± 0.15 mm). The thickness decreases toward the limbus (0.50 ± 0.11 mm), the ora serrata (0.43 ± 0.14 mm), and the equator (0.42 ± 0.15 mm) and is the thinnest at the peripapillary scleral flange (0.39 ± 0.09 mm) (14). The relatively small inter-individual variability in scleral thickness supports a standardized approach to injections, allowing clinicians to use a uniform microneedle length. For most cases, a 0.9 mm microneedle suffices, while certain scenarios may require a slightly longer 1.1 mm microneedle (15,16). This finding simplifies the suprachoroidal injection procedure, as it reduces the need for individualized microneedle length adjustments based on patient-specific ocular characteristics.

Suprachoroidal Space

The SCS is a potential area nestled between the sclera and the choroid (Figure 3) [17]. This space is often in close contact due to the intraocular pressure (IOP) and the presence of attaching fibers [18]. However, the introduction of fluid, whether internally or externally, can transform this potential space into a more defined one

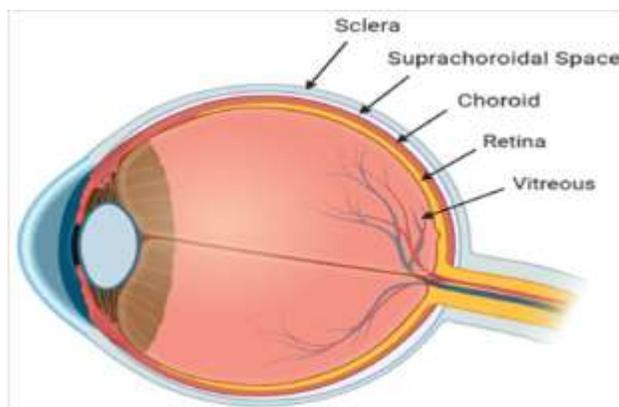


Figure 3: Anatomy of the Suprachoroidal Space and Posterior Segment

The SCS, located between the sclera and choroid, has boundaries that are anatomically distinct. Anteriorly, the SCS extends up to the scleral spur, a pivotal landmark that marks the juncture of scleral attachment to the ciliary body. Posteriorly, the SCS is situated near the optic nerve and short posterior ciliary arteries (3,12, 18) It is essential to recognize the anatomical placement of the SCS when considering pharmacological interventions, such as SC injections. Distinguishing the SCS from the subretinal space is crucial, as the former lacks the immune privilege characteristic due to its position outside the blood–retinal barrier. For clarity, it is worth revisiting the structure

of the blood–ocular barrier. This barrier consists of the vascular endothelium of the retina, which is non-fenestrated and bound by tight junctions. Although the choroidal vessels are fenestrated, the barrier is maintained through the presence of tight junctions within the retinal pigment epithelium (RPE) [3,12,18].

The SCS has shown considerable expansion following the injection of certain drugs in this area. A study involving the injection of triamcinolone acetonide in the SCS demonstrated a notable increase in mean SCS width, from 9.9 μm to 75.1 μm [7]. This expansion proved the influence of SC injection in manipulating the SCS's physical attributes. However, the increase was temporary, with the SCS width returning to approximately 14.9 μm a month after the final injection, revealing no lasting impact on the SCS's anatomy [7].

Routes of Administration-

Numerous routes are available for administering ocular medications, each with unique strengths and weaknesses. Standard methods include systemic delivery (e.g., oral, intravenous, and subcutaneous routes) and local delivery methods (e.g., topical eye drops, periocular or IV injections, and IV implants). Figure 4 will effectively represents Overview of Various Ophthalmic Medication Delivery Routes

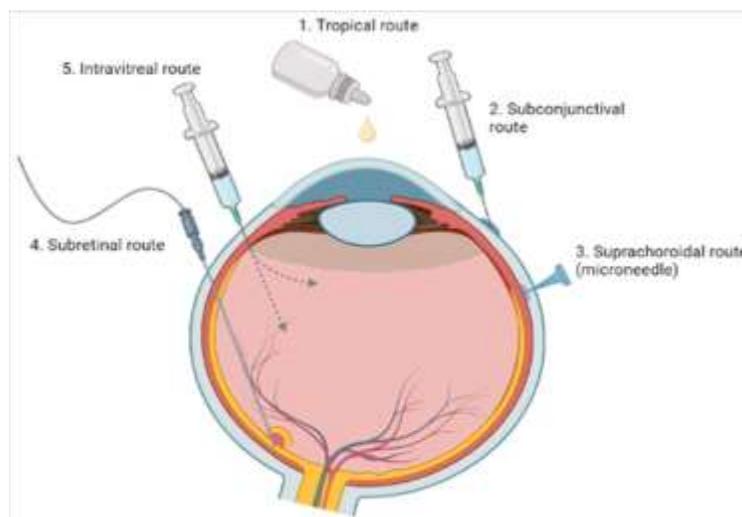


Figure 4: An Overview of Various Ophthalmic Medication Delivery Routes

This figure 4 illustrates the range of administration methods used in ophthalmic medicine, including topical, subconjunctival, intravitreal, suprachoroidal, and subretinal techniques. While these methods can be effective, they can also come with certain limitations [19]. An overview of the advantages and disadvantages associated with each ocular drug administration method is summarized in table.

Table 1: Comparison of Different Ocular Drug Administration Methods and Figure 4 [2,20].

Injection Method	Advantages	Disadvantages
Topical Eye Drops (21)	<ol style="list-style-type: none"> 1. Non-invasive method for ocular drug delivery 2. Prevalent, well-known method 	<ol style="list-style-type: none"> 1. Low bioavailability to posterior segment tissues 2. Short duration of action, requiring frequent administration 3. Local complications (ocular surface irritation, cataracts, ocular hypertension, periocular aesthetic issues)
Systemic Drug Administration	<ol style="list-style-type: none"> 1. Noninvasive and potentially patient-preferred 2. Usable as standalone or in combination with topical delivery 	<ol style="list-style-type: none"> 1. Systemic side effects due to high dosage, necessitating safety and toxicity considerations 2. High doses often required due to reduced accessibility to targeted ocular tissues 3. Effective bioavailability is challenging due to blood-ocular barriers
Subretinal Injection (22)	<ol style="list-style-type: none"> 1. Targeted treatment for the RPE and outer retina 2. Reduced immune reactions for gene therapy using viral vectors (due to injection in an immune-privileged site) 	<ol style="list-style-type: none"> 1. Limited distribution of injectate within subretinal space; effects confined to injection site 2. Invasive procedure, requires vitrectomy
Intravitreal Injection (23)	<ol style="list-style-type: none"> 1. Rapid therapeutic onset 2. Fewer systemic side effects compared to oral or IV administration 	<ol style="list-style-type: none"> 1. Local complications (increased IOP, cataract formation) 2. Systemic absorption and side effects can still occur 3. Possible post-injection floaters

Topical Administration-

Topical administration, often in the form of eye drops, is a prevalent non-invasive method for ocular drug delivery. However, it is associated with several challenges as a consequence of the anatomy and physiology of the eye.

First, the concentration gradient from the tear reservoir to the cornea or conjunctiva drives passive absorption, but only approximately 20% of a drop (about 10 μ L of the 50 μ L drop) is retained in the eye (24) Within 3 - 4 min, half of the administered medication has typically left the eye, with a turnover rate of roughly 15% per minute. Factors such as reflex tearing, consecutive dosing, and the small cul-de-sac of the eye contribute to a fast tear turnover time, further accelerating drug clearance and challenging the effective drug absorption (1,2)

Due to the relatively impermeable corneal barriers and high tear turnover rates, topical administration often necessitates frequent, high-dose applications. This approach can cause local and systemic side effects, potentially reducing patient compliance (25). Remarkably, studies have indicated that the rate of medication non-compliance in the general population is approximately 80% (26)

Additionally, the exposure of unaffected tissue to drugs may lead to certain side effects. For instance, chronic usage of topical steroids can result in complications such as cataracts and ocular hypertension (23) similarly; topical prostaglandins can lead to undesirable periocular aesthetic concerns (27)

Systemic Administration-

The oral route to be effective in ocular applications, high oral bioavailability is a key requirement. Furthermore, following oral absorption, molecules must navigate through systemic circulation and across the blood–ocular barriers, notably the blood–aqueous and blood–retinal barriers (Figure 5). The blood–retinal barrier is further stratified into an inner barrier, protected by the fenestrated endothelium of retinal vasculature, and an outer barrier, upheld by tight junctions within the RPE. The functional properties and inherent barriers posed by these protective ocular structures represent significant challenges for the systemic drug administration [28, 29].

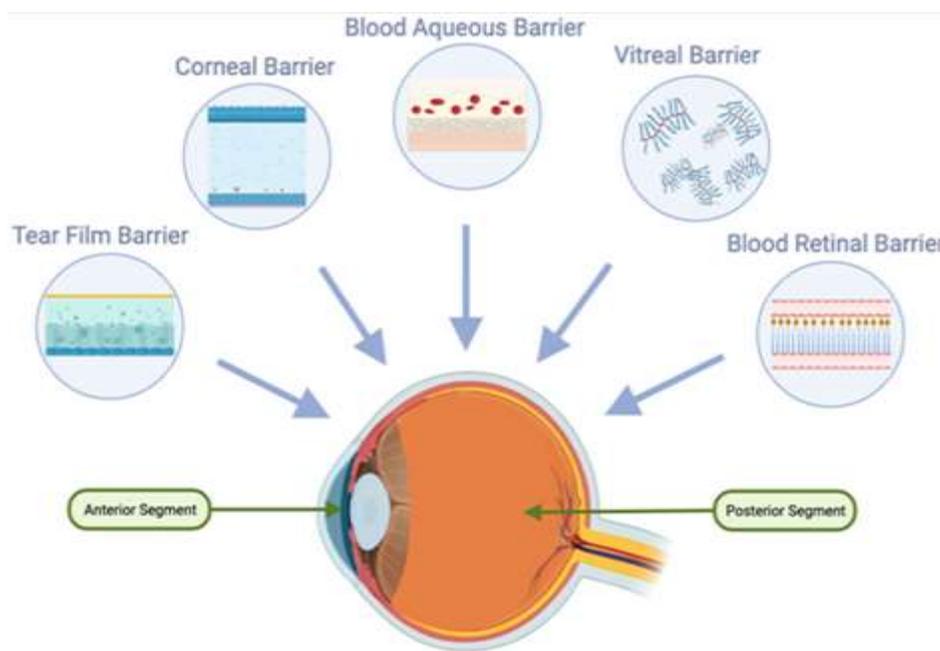


Figure 5: Anatomical and Physiological Barriers in the Eye Impacting Drug Delivery.

For instance, systemic medications, such as steroidal and nonsteroidal anti-inflammatory drugs and biologic and nonbiologic immunomodulatory agents, can effectively treat uveitic macular edema

(UME) but are often recommended for bilateral disease or cases resistant to local therapy due to AEs such as infections and GI disturbances

Periocular Injection

Despite numerous scientific efforts, delivery of therapeutic amounts of a drug to the retina remains a challenge. This challenge is compounded if chronic therapy is desired. The inability or inefficiency of topical and systemic routes for retinal delivery of existing drugs is now widely accepted. Although the intravitreal route offers high local concentrations in the vitreous and, hence, retina, these advantages are offset by side effects, such as cataracts, endophthalmitis and retinal detachment, following repeated intravitreal injections, or intravitreal placement of sustained-release implants. As discussed in this review, periocular routes, including subconjunctival, sub-tenon, retrobulbar, peribulbar and posterior juxtасlеral routes, potentially offer a more promising alternative for enhanced drug delivery to the retina compared with topical and systemic routes. Periocular routes exploit the permeability of sclera for retinal drug delivery, and they are particularly useful for administering sustained-release systems of potent drugs. This review discusses the various periocular routes with respect to their anatomical location, pharmacokinetics, safety and mechanisms of drug delivery. In the coming years, several innovations in absorption enhancement, drug delivery systems and drug administration devices are anticipated for improving retinal drug delivery via periocular routes (2)

Intravitreal Injection

In the realm of ocular drug delivery, IV administration offers numerous advantages and has been widely adopted as a first-line therapy for conditions such as neovascular age-related macular degeneration (nAMD) [30], diabetic macular edema (DME)(31)

Diabetic macular edema (DME) is one of the leading causes of vision loss in patients with diabetic retinopathy [1, 2]. In addition to intensive glycemic control, the management of DME requires multidisciplinary care, including intravitreal anti-vascular endothelial growth factor (VEGF) drugs, intravitreal corticosteroids, laser photocoagulation, and vitrectomy (32,33). Currently, intravitreal anti-VEGF drugs are mostly regarded as first-line therapy (34). With the increasing recognition of the role of inflammation in DME, intravitreal corticosteroids have been developed (35) Corticosteroids can inhibit several cytokines and chemokines , reduce retinal neovascularization and permeability (35) and have substantial anatomical and functional benefits for DME patients (36)

However, IV injections are not without certain drawbacks and potential complications. Severe complications can occur, which include the risk of endophthalmitis, retinal detachment, and

vitreous hemorrhage. Furthermore, IV steroids specifically have associated complications such as increased intraocular pressure and cataract development (37) Minor side effects and inconveniences, such as floaters post-injection and the potential for systemic absorption and resultant side effects, can also adversely affect patient satisfaction and treatment adherence (37)

Subretinal Injection

Subretinal delivery presents a compelling avenue for retinal gene therapy, especially for the treatment of retinal degeneration and vascular diseases. This approach involves the direct introduction of viral vectors into the subretinal space an immune-privileged site thus allowing targeted treatment for the RPE and outer retina while reducing the likelihood of immune reactions (22)

Many current retinal gene therapy protocols employ subretinal injection of the AAV vector, which involves vitrectomy surgery and insertion of a cannula through the retina to create a retinotomy to deliver the viral particles to photoreceptors and/or underlying retinal pigment epithelium (RPE). Compared to systemic delivery, AAV in the subretinal space elicits a reduced immune response compared to systemic delivery, similar to the anterior chamber-associated immune deviation (ACAID) that enables corneal transplantation without immunosuppression.(39,40) However, the limitations of this technique is more difficult and subject to potential complications of vitrectomy surgery such as retinal tear, retinal detachment, the need for more eye surgery, cataract, intraocular pressure abnormalities, and intraocular infection.(41) However, it is important to note that subretinal delivery does have its own set of challenges. It is invasive in nature, requiring a vitrectomy for administration. Moreover, the localized nature of the injectate can limit its distribution within the subretinal space, potentially confining the therapeutic effects to the area surrounding the injection site (42)

SUPRACHOROIDAL INJECTION: RATIONAL

Suprachoroidal drug delivery has been demonstrated to be a reliable and consistent drug delivery method for targeted treatment of retinal and choroidal disorders to potentially maximize efficacy, while compartmentalizing therapies away from the unaffected tissues to potentially enhance safety. These delivery attributes, along with fluid transport properties and formula customization for pharmacological agents, may allow for more tailored treatment of diseases affecting chorio-retinal tissues.(43)

Advantages over the Intravitreal Injection-

SC injection stands out as a method that enables precise and targeted delivery to the retina, RPE, and choroid. By bypassing barriers such as the ILM and vitreous, which are commonly

encountered in the IV drug administration (44) this method achieves broader bioavailability across the diseased retina and choroid (42,45)

The unique compartmentalization provided by SC injection within the SCS plays a pivotal role in its advantages. This containment restricts drug exposure to target tissues, minimizing unnecessary contact with the anterior segment (42,44) which, in turn, reduces the risk of complications such as cataract formation and elevated intraocular pressure (22) . Furthermore, this compartmentalization minimizes systemic absorption, leading to fewer systemic side effects (22) Supporting these benefits, a 2022 study involving rabbits demonstrated that SC delivery of TRIESENCE provided a 12-fold greater exposure to the RPE, choroid, sclera, and retina compared to IV delivery(22)

Moreover, SC injection offers a sustained-release mechanism, reducing the frequency of injections and, consequently, the number of patient appointments (42)

Advantages over Subretinal Injection-

When compared to subretinal injection, the SC method can be administered in an outpatient setting, reducing the need for complex surgical procedures such as vitrectomy (42,45) Furthermore, it offers the potential to provide a broader distribution of drugs across the posterior segment (44)

Drug Suspension Size and Formulation Viscosity

Current research is exploring the potential to alter drug suspension size and formulation viscosity in order to adjust the duration and distribution of the injected drugs. This flexibility could allow precise tailoring of drug delivery, ensuring that the right amount of medication reaches the target location.

Cost-Effectiveness

Over a 10-year horizon, a simulated US adult patient-level model evaluated the costeffectiveness of suprachoroidal triamcinolone acetonide (SC-TA) compared to the best supportive care for UME derived from the PEACHTREE trial. The authors determined that, at willingness-to-pay thresholds of \$50,000 or more (2020 US dollars) per quality-adjusted life-year gained, SCTA was a cost-effective procedure (46) The combined practicality, enhanced safety profile, proven efficacy, targeted delivery, and durability offered by SC drug delivery have made SC injections an innovative treatment modality for diverse ocular conditions. This underlines the imperative for more extensive research into this therapeutic strategy, which is also the focus of this review article.(47)

CONCLUSION:

In conclusion, the review underscores the formidable challenges encountered in delivering

effective treatments to the intricate structures of the eye's posterior segment. The limitations of current modalities, marked by issues of penetration, residence time, and bioavailability, underscore the critical need for innovative solutions. Suprachoroidal injection has emerged as a promising and novel approach, offering a minimally invasive route for targeted drug delivery. The advantages of suprachoroidal injection, including higher drug concentrations, improved bioavailability, and prolonged therapeutic effects, make it a potential game-changer in the management of posterior segment eye diseases. Notably, the method presents a notable reduction in the risk of adverse events, particularly those associated with corticosteroid-related complications, contributing to improved patient safety. While the review highlights the potential of suprachoroidal injection, it also emphasizes the necessity for continued research to address existing challenges. Technological advancements and refinement of injection techniques are crucial, as are considerations of cost and accessibility. Furthermore, exploring collaborative strategies with biotech products, gene therapies, and cell-based treatments holds promise for unlocking personalized and highly effective therapeutic interventions. In essence, the potential of suprachoroidal injection to overcome anatomical barriers and enhance therapeutic outcomes in posterior segment eye diseases is evident. With ongoing research and technological innovations, this approach holds significant promise for revolutionizing the landscape of ocular drug delivery and advancing personalized treatments for improved patient outcomes.

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