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Clinical Characterization of Suprachoroidal Injection Procedure Utilizing a Microinjector across Three Retinal Disorders

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Purpose: This study assessed physician-investigator experience with suprachoroidal (SC) injections, an investigational therapeutic administration technique using a 900 or 1100 µm microneedle to inject drugs into the SC space.

Methods: Datasets from six clinical trials across three diseases (noninfectious uveitis; diabetic macula edema, and retinal vein occlusion) were assessed. In addition to a user survey, retrospective correlations were performed between procedural variables (needle length), and demographics, and ocular characteristics.

Results: In the user survey, 84% (31/37) of physician-investigators did not perceive the SC injections to be meaningfully more challenging than other ocular injections. For the correlation analysis, the 900 µm needle was used for 71% (412/581) of baseline injections, and switching to the longer needle occured in the remaining 29% of baseline injections. No statistical correlations were found between needle lengths and age, race, disorder, refraction, visual acuity, intraocular pressure, retinal central subfield thickness, or lens status. Patient gender and needle length were statistically associated, with 76% (210/275) versus 66% (202/306) of injections administered with 900 µm needles for female and male gender, respectively. Injection quadrant correlated to needle length with 78% (214/275) of superotemporal quadrant injections administered with 900 µm needles, compared with 65% (73/113) of inferotemporal quadrant injections.

Conclusions: Both the user survey and the correlation analysis demonstrated that SC injection is well accepted by physician-investigators, and the two needle lengths accommodate a wide range of anatomic and demographic variables.

Translational Relevance: These results, along with the presented ex-vivo endoscopic imaging, suggest that SC injection could be readily adopted in clinical practice for targeted compartmentalized delivery of ocular therapeutics.

Introduction

Common causes of irreversible blindness include age-related macular degeneration (AMD), diabetic retinopathy (DR), retinal vein occlusion (RVO), and uveitis.[1,2] Although frequent intravitreal injections of anti-vascular endothelial growth factor-A (anti-VEGF-A) agents or corticosteroids have achieved dramatic results in randomized clinical trials,[3–15] "real world" outcomes fall short of these results, due in part to undertreatment, demonstrating unmet need for more effective durable treatment.[16–18] This problem is of particular importance because of the rising prevalence of diabetes with the ensuing DR, as well as an increasing elderly population with the attendant increase in AMD.[1]

Figure 1. Key suprachoroidal injection techniques. The needle must be inserted perpendicularly to the ocular surface because the free needle length is on the order of the thickness of the sclera. The needle hub is designed to compress on the ocular surface to reduce the thickness of the conjunctiva and to form an indentation. Because the SCS, a potential space, is opened as the injection occurs, slow injection is essential once loss of resistance is experienced. It is recommended for the physician to first attempt the SC injection with the shorter needle. The two needle lengths of 900 µm and 1100 µm are offered to accommodate variations in patient anatomy. If persistent resistance is felt, then the longer needle may be used to complete the injection, after ensuring appropriate injection technique.

Suprachoroidal (SC) injection with a microneedle-based technology, such as the SCS Microinjector (R) (Clearside Biomedical, Alpharetta, GA), is a novel approach currently undergoing clinical investigation in conjunction with therapeutic agents which are delivered to chorioretinal structures (Fig. 1).[19] There are three potential advantages of SC injections, compared to standard intravitreal injections. First, when drug is administered into the suprachoroidal space (SCS), the injectate flows posteriorly and circumferentially. This allows for preferential targeting of affected posterior segment tissue layers as demonstrated in animal studies. Second, this ocular distribution pattern facilitates compartmentalization within the SCS, minimizing exposure to the anterior chamber and the vitreous, with the potential for safety benefits.[20] Lastly, sustained duration and favorable pharmacokinetics have been observed for small molecule suspensions, with the potential to reduce treatment burden.[21] As a proof of concept, suprachoroidally administered CLS-TA, an investigational formulation of 4 mg of triamcinolone acetonide (Clearside Biomedical, Alpharetta, GA), has undergone clinical trial for the treatment of noninfectious uveitis (NIU), diabetic macula edema (DME), and RVO (CR Henry et al. Unpublished data. 2020).[22–25] In a Phase 3 trial for uveitic macular edema, suprachoroidally administered CLS-TA demonstrated efficacy and a favorable safety profile,[25] with lower incidences of intraocular pressure (IOP) elevation, exacerbation of glaucoma and cataract development compared to the literature results of intravitreal or periocular corticosteroid injections.[26–33] Additional clinical trials are planned to suprachoroidally administer other therapeutic agents, including gene therapy for neovascular AMD and DR,[34] viral-like particles for choroidal melanoma[35] and a tyrosine kinase inhibitor for neovascular AMD.[36] However, the clinical literature on the SC delivery procedure is limited.

The SC injection procedure with the SCS Microinjector distinctly differs from an intravitreal injection procedure. To accommodate anatomic variations in patient ocular anatomy, the SCS Microinjector is supplied with two 30G microneedles with free lengths of 900 and 1100 µm. Injections are recommended to be first attempted with the shorter needle. When the needle tip penetrates through the sclera, the injectate flows into and expands the SCS, accompanied by intraprocedural tactile feedback of loss of resistance. If persistent resistance is felt, the injection needle is switched to the longer 1100 µm needle.

This study employed two methods to assess physician-investigator experience with the procedure, after the physician-investigator had received training and administered a SC injection in clinical trials. First, results from a user experience survey were assessed. Second, retrospective correlations were performed between procedural variables, defined as the two needle lengths, and characteristics involving both demographics and ocular status.

Methods

Survey Collection

All clinical trials described herein were conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline and the Declaration of Helsinki; institutional review board committee approval was obtained. All study patients provided informed consent. A user questionnaire was completed in one Phase 3 clinical trial for NIU, AZALEA (NCT03097315), to capture procedural details and user acceptance. In particular, feedback on the injection procedure, the volume of injectate dispensed from the syringe, and switching dynamics from the 900 µm needle to the 1100 µm needle were collected.

Clinical Data Collection

Clinical data were collected and aggregated from all study case report forms (CRF). Six clinical trials were included in this post-hoc analysis: two Phase 3 trials for NIU—AZALEA and PEACHTREE (NCT02595398), one Phase 2 trial for DME—TYBEE (NCT03126786), one Phase 2 trial for RVO—TANZANITE (NCT02303184) and two Phase 3 trials for RVO—SAPPHIRE (NCT02980874) and TOPAZ (NCT03203447). In all six trials except TANZANITE, study protocols included more than one possible SC injection. To minimize physician-investigator bias from the subsequent injections in a particular patient, only the baseline injection from each patient was included in the analysis related to needle length usage. Physician-investigators indicated the needle length used during the injection in response to the clinical procedure note prompt "Needle length used for Injection (900 or 1100 µm)" during each administration.

Demographic features extracted from the databases included age, gender, and race. Ocular characteristics examined from the database included diagnoses, best corrected visual acuity (BCVA), IOP, lens status, Early Treatment Diabetic Retinopathy Study (ETDRS) refraction, retinal central subfield thickness (CST), and injection quadrant.

Neither scleral thickness nor axial lengths were assessed within the studies, but a retrospective subgroup analysis was conducted assessing degree of myopia as a potential factor in needle length usage, using the spherical equivalent based on ETDRS refraction as an indirect correlate of the level of myopia. This subgroup analysis included 40 patients from four physician-investigators participating in AZALEA, PEACHTREE, SAPPHIRE, and TOPAZ described above, as well as HULK (NCT02949024), a phase 1 clinical trial in DME. Spherical equivalent values were calculated based on baseline refraction values, derived during protocol BCVA assessments. Pseudophakic and aphakic patients were excluded from the subgroup analysis.[37]

Statistical Analysis

Retrospective correlations were performed between procedural variable, defined as the two needle lengths, the demographic characteristics and ocular status. Multiple statistical methods were deployed. For univariate analysis, standard analysis of variance was used for all continuous variables and Pearson's χ^2 test for attribute data. A P value ≤ 0.05 was considered statistically significant. No adjustments were made for multiple testing.

Biserial correlation was conducted to identify correlations between quantitative variables and the binary variable of the two needle options. Ranked biserial correlation was also performed as a sensitivity measure, where the correlation was conducted using a ranked score, as opposed to the actual measurement of the continuous variable. This is an alternative method with the aim to reduce the impact of outliers. For the biserial correlation and ranked biserial correlation, the correlation value could range from −1 (perfectly negative correlation) to 1 (perfectly positive correlation).

Multivariate logistical regression analysis was conducted. The following independent variables were included in the model: age, baseline BCVA, baseline CST, IOP, lens status at baseline, gender, race and quadrant of administration. The validity of the regression model was evaluated per the goodness-of-fit test, as well as the likelihood ratio test.

Results

User Survey Revealed High Level of Acceptance of SC Injections

A user experience survey was completed in AZALEA, as summarized in Table 1. In this survey, both the physician-investigator and an in-room observer answered a series of questions evaluating the SC injection procedure, from filling drug into the device to assessing the actual injection, such as the perceived force necessary for the injection. In this survey, all physician-investigators attempted the injection with the 900 µm needle first, as directed by the clinical procedure protocol. No needle change was required

Table 1. Summary of User Survey from Baseline Injection

	Yes	No
Did the physician use the 900 µm needle first? *(completed by in-room observer)*	100% (38/38)	0% (0/38)
Did you need to change needles?	39.5% (15/38)	60.5% (23/38)
Were you able to inject all of the contents of the syringe?	100% (38/38)	0% (0/38)
In your experience, did the suprachoroidal injection procedure present any new challenges as compared to other types of injections?[a]		
Completed injection with 900 µm	4.5% (1/22)	95.4% (21/22)
Completed injection with 1100 µm	33.3% (5/15)	66.7 % (10/15)
Did you have difficulty with any of the steps in the procedure?		
Completed injection with 900 µm	0% (0/23)	100% (23/ 23)
Completed injection with 1100 µm	33.3% (5/15)	66.7% (10/15)
	Acceptable	Not Acceptable
How do you rate the force necessary for the injection?	89.5% (34/38)	10.5% (4/38)
Completed injection with 900 µm	95.7% (22/23)	4.3% (1/23)
Completed injection with 1100 µm	80.0% (12/15)	20.0% (3/15)

[a]One physician-investigator omitted the question.

for 60.5% (23 of 38) SC injections at baseline based on physician survey. In all 15 instances that a needle change was required, this was only after demonstrable inability to complete the injection with the 900 µm needle (shorter needle option), as determined by the physician-investigator. In all these instances, the injection was subsequently administered and completed with the 1100 µm needle. No inadvertent intravitreal injections were reported. When physician-investigators were asked to rate the force necessary for the injection (acceptable or not acceptable), 95.7% (22 of 23) physician-investigators who completed the injection with the 900 µm needle rated the force as acceptable; 80% (12 of 15) who had to switch to the 1100 µm needle to complete the injection rated the force as acceptable. All physician-investigators who completed the injection with the 900 µm needle indicated that they had no difficulty with any of the steps in the procedure (yes or no). Of the physician-investigators who completed the procedure after switching to the 1100 µm needle, 66.7% (10 of 15) indicated that they had no difficulty with the overall procedure. In all 38 injection procedures, the physician-investigators reported that they were able to inject all the contents of the syringe with the two needles that were provided for the injection procedure. Lastly, physician-investigators were also asked if the SC injection procedure presented any new challenges as compared to other types of injections (yes or no); 95.4% (21 of 22) of the physician-investigators who completed the procedure with the 900 µm needle responded that the SC injection procedure did not present new challenges; one physician did not answer the question and one stated that the procedure was more challenging as the physician-investigator perceived that the patient had more discomfort than typical intravitreal injections. For injections that were completed after switching to the 1100 µm needle, 66.7% (10 of 15) of the physician-investigators indicated the SC injection procedure was not more challenging. For the injections that were considered to be more challenging, the following rationales were noted: "steps to decide when to switch needle, difficult injection due to soft eye, injection was not smooth, and injection location had to be moved from inferotemporal quadrant to superotemporal quadrant".

SC Injection Procedure Shows Consistency Across Demographic and Ocular Characteristics

There were 133, 36, and 412 patients with NIU, DME, and RVO, balanced by gender, with mean age of 50.8, 59.8, and 65.4 years old, respectively. A total of 1274 SC injections across six clinical trials were performed and 581 baseline injections were included in this analysis. Physician-investigators reported that the 900 µm needle was used to administer study drug in 412 procedures (70.9%) and the 1100 µm needle was used to administer study drug in 169 procedures (29.1%). Among all evaluated variables (disorder,

Table 2. Correlations Between Procedural Variables (900 µm vs 1100 µm needles) and Demographics or Ocular Characteristics (Univariate Analysis)

	Total Sample Size[a]	900 µm	1100 µm	*P* Value
Disorder variables				
Noninfectious uveitis	133	98 (74 %)	35 (26 %)	0.504[b]
Diabetic macular edema	36	23 (64 %)	13 (36 %)	
Retinal vein occlusion	412	291 (71 %)	121 (29 %)	
Patient-specific variables				
Spherical equivalent	40	−0.86 (2.613)	−1.13 (2.113)	0.760[c,d]
IOP (Pre-SC Injection)	581	17.6 (4.70)	18.2 (5.36)	0.199[c]
Lens status - phakic	138	103 (75 %)	35 (25 %)	0.270[b]
Lens status - pseudophakic	443	309 (70 %)	134 (30 %)	
Gender - female	275	209 (76 %)	66 (24 %)	0.006[b]
Gender - male	306	202 (66 %)	104 (34 %)	
Age	581	61.5 (14.04)	62.2 (14.69)	0.625[c]
Race				
White	378	262 (69 %)	116 (31 %)	0.247[b]
Non-white	203	150 (74 %)	26 %)	
SC injection variables (quadrant)				
Superior Temporal	275	214 (78 %)	61 (22 %)	<0.001[b]
Superior	47	36 (77 %)	11 (23 %)	
Temporal	90	62 (69 %)	28 (31 %)	
Inferior Temporal	113	73 (65 %)	40 (35 %)	
Inferior	34	17 (50 %)	17 (50 %)	
Superior Nasal	14	7 (50 %)	7 (50 %)	
Nasal	0	0	0	
Inferior Nasal	8	3 (38 %)	5 (62 %)	

[a]Sample size represents baseline injections.
[b]*P* value based on Pearson's χ^2 test.
[c]*P* value based on a one-way analysis of variance.
[d]Phakic patients only.

refraction, intraocular pressure (IOP), lens status, gender, age, race, and quadrant of administration), statistical significance was only observed in gender and quadrant of administration (Table 2). Evaluating by gender, the 900 µm needle was used for 76% (209 of 275) of the female patients compared to 66% (202 of 306) of the male patients (Fig. 2). Furthermore, there was a statistically significant correlation between the needle usage and the administration quadrant: the 900 µm needle was used for 78% of injections administered in the superotemporal quadrant, compared to 65% of the injections in the inferotemporal quadrant (Fig. 2). No differences in needle usage were noted with spherical equivalent, IOP, disorder, age, lens status, or race. Biserial correlation also revealed little correlation between needle length and the continuous variables, such as age and baseline IOP.

Multivariate logistical regression included age, BCVA, IOP, CST, lens status, gender, race and quadrant of administration as the regressors. The results corroborated with previous univariate analysis that only gender and quadrant of administration correlated with needle length.

Discussion

Unlike intravitreal injections, in which the drug is injected into the relatively large space of the vitreous chamber, SC injections rely on expanding the potential space as the drug is injected between the sclera and the choroid. Ex vivo imaging, visualized externally or through dissection, demonstrates that fluid spreads posteriorly and circumferentially in the SCS.[38,39] The

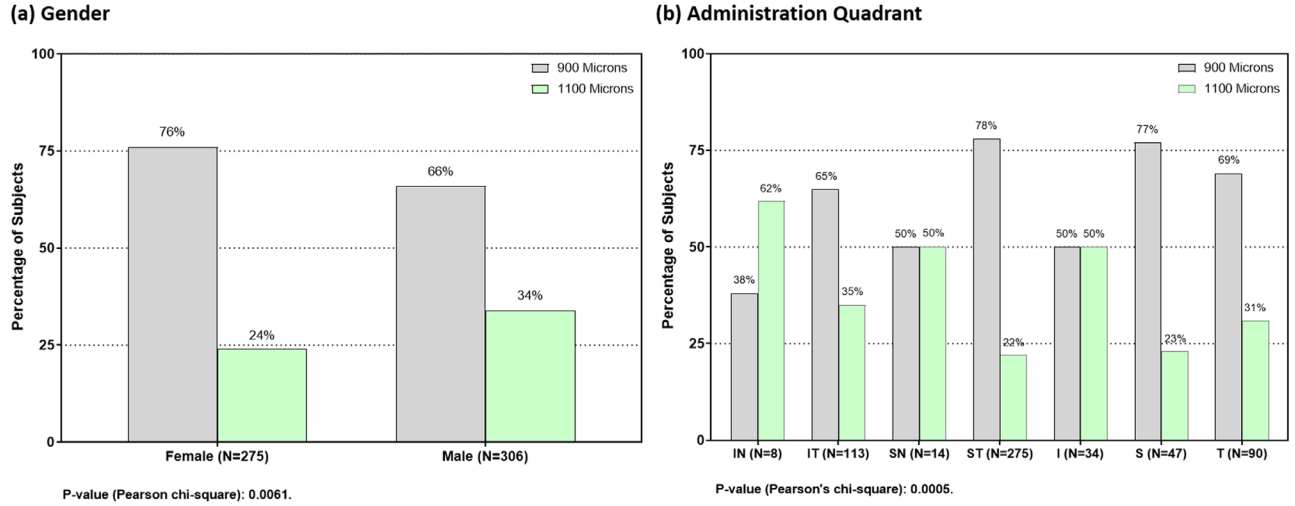

Figure 2. Correlations between procedural variables (900 µm vs. 1100 µm needles) and (a) gender or (b) administration quadrant (univariate analysis). Among all evaluated variables (disorder, refraction, IOP, lens status, gender, age, race, and quadrant of administration), statistical significance was only observed in (a) gender and (b) quadrant of administration. Evaluating by gender, the 900 µm needle was used for 76% (209 of 275) of the female patients compared to 66% (202 of 306) of the male patients. Furthermore, there was a statistically significant correlation between the needle usage and the administration quadrant: the 900 µm needle was used for 78% of injections administered in the superotemporal quadrant, compared to 65% of the injections in the inferotemporal quadrant.

SCS expansion due to fluid flow has also been observed on anterior optical coherence tomography demonstrating increased SCS thickness from 9.9 µm immediately before injection to 75.1 µm 30 minutes after SC injection.[40]

During the injection procedure, access to the SCS is confirmed by intraprocedural loss of resistance, at which point injectate flows into the SCS circumferentially and peripherally. One critical factor for successful SC injections is the needle length, which needs to be sufficiently long to pass through the sclera without penetrating through the retina or the vitreous. To accommodate anatomic variation in scleral thickness, the SCS Microinjector includes two needle lengths, and users are trained to start with the shorter needle and switch to the longer needle if the SCS cannot be accessed. During training, physician-investigators are taught how resistance in the device corresponds to the needle tip location and can be used to guide the injection. When the needle tip is located within the sclera, users will feel resistance from the plunger, preventing off-target drug delivery. When the needle tip is advanced beyond the sclera, into the SCS, users will feel a loss of resistance and the plunger will readily advance smoothly and easily to inject drug into the SCS. If loss of resistance, and therefore an injection, cannot be achieved with the 900 µm needle, the longer needle should be used. Endoscopic imaging with enucleated porcine eyes demonstrates that the needle tip remains in the SCS during the entire injection (Fig. 3). In addition to preclinical data, the current analysis demonstrates that SC injections can reliably be administered in multiple clinical trials for multiple disorders with the two different needle lengths (900 µm and 1100 µm) that are offered, accommodating for potential patient variabilities such as variation of scleral thickness.

The literature confirms that scleral thickness varies along the anterior-posterior axis, gradually decreasing from the scleral spur to the equator and then increasing from the equator to the optic nerve.[41] With conditions such as myopia, additional scleral thinning can be observed associated with axial elongation.[42–44] In our analysis, spherical equivalent in phakic patients, used as a surrogate marker for degree of myopia, did not correlate with needle length usage. Three factors may contribute to this finding. First, most of the scleral thinning attributable to myopia occurs closer to the equator or in the posterior segment of the eye, rather than the pars plana, where SC injections are administered.[41,45] Second, in the clinical trial dataset, patients with high myopia, defined more than −6 diopters or at the discretion of the physician-investigator, were excluded from the trials, limiting the generalizability of the analysis results. Lastly, degree of myopia, measured by spherical equivalent as a surrogate, may not be completely related to axial length, but due to corneal or lenticular variations.

Scleral thickness also varies, to a lesser extent, by quadrant. In the NIU trials, the superior temporal quadrant was recommended, and for the remaining trials the temporal hemisphere was recommended. At

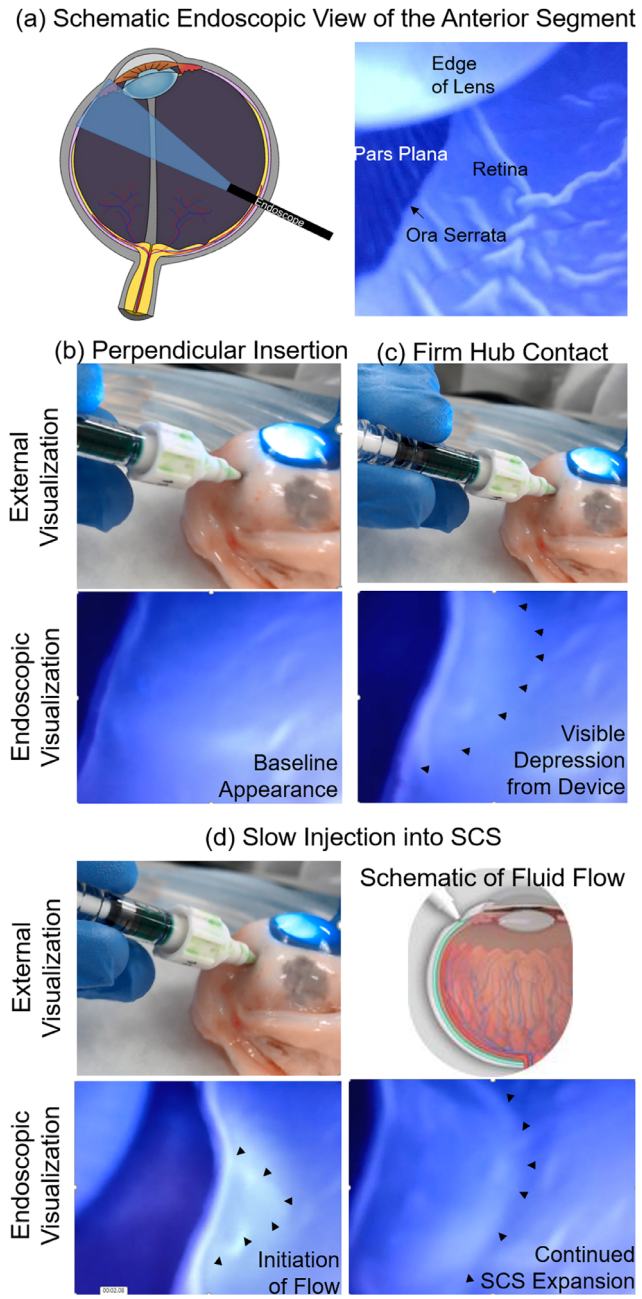

Figure 3. Ex vivo endoscopic visualization of SC injection. For endoscopic view setup, enucleated porcine eyes were inflated to an appropriate intraocular pressure by maintaining a 20-cm water column. An aqueous-based green dye was used for easy external visualization. (a) Schematic (image updated from Andrew Meyerson, distributed under a CC-BY-SA-3.0 license) and endoscopic view. (b–d) SC injection visualized externally and internally. (b) Before injection, a smooth, uncompressed inner retinal surface was observed. (c) As pressure was applied from the needle hub to form a dimple externally, a smooth deformation was observed internally. The needle tip, as a sharp point, was not observed. (d) As the SCS was accessed, injectate was immediately observed to flow posteriorly and circumferentially. The *black arrowheads* highlight the fluid boundary as it expands the SCS.

the pars plana, the sclera is thicker at the inferior quadrant compared to the superior quadrant and thicker at the nasal quadrant compared to the temporal quadrant.[46] The average difference in thickness between the inferior and superior quadrants is approximately 200 µm. This difference may represent as a contributing factor to the correlation found between needle length and administration quadrant, because the use of the longer needle was more commonly required in the inferior temporal versus the superior temporal quadrant.

Gender was also found to statistically correlate with selected needle length. This may be due to differences in overall average stature between male and female patients. However, body mass index or other similar data were not collected, and therefore this possible confounding factor cannot be further investigated retrospectively or controlled. Furthermore, previous studies suggested no correlation between scleral thickness and gender.[41]

Limitations of this study include its retrospective nature and small sample size for certain subgroup analyses, such as refraction and lack of applicability to high myopes because they were excluded from the trials. Nevertheless, this study demonstrates that the SC injection procedure shows consistency across various demographic (age, race) and ocular characteristics (disorder, BCVA, IOP, lens status, CST). The user survey also reflected a high level of acceptance and relative ease of use by physician-investigators. In the needle length correlation analyses, while there were small correlations between needle length and both injection quadrant and gender, these retrospectively-identified correlations are not sufficiently robust for treatment guidance in selecting the initial needle to perform SC injection; starting with the shorter needle length (900 µm) remains the recommended treatment option to maximize patient safety, reproducibly targeting the SC space, while minimizing the risk of an inadvertent intravitreal injection. This is particularly prudent for novel therapeutic agents, such as gene therapy or novel tyrosine kinase inhibitors with less well-known safety profiles. In conclusion, this analysis demonstrates that the SC procedure, which have been performed over a thousand times in clinical trials, can be performed reliably and is well accepted by physician-investigators.

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