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SCORE Study Report 7: Incidence of Intravitreal Silicone Oil Droplets Associated With Staked-on Versus Luer Cone Syringe Design

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Abstract

PURPOSE—To evaluate the incidence of intravitreal silicone oil (SO) droplets associated with intravitreal injections using a staked-on versus luer cone syringe design in the **S**tandard Care versus **CO**rticosteroid in **RE**tinal Vein Occlusion (SCORE) Study.

DESIGN—Prospective, randomized, phase III clinical trial.

METHODS—The incidence of intravitreal SO was compared among participants exposed to the staked-on syringe design, the luer cone syringe design, or both of the syringe designs in the SCORE Study, which evaluated intravitreal triamcinolone acetonide injection(s) for vision loss secondary to macular edema associated with central or branch retinal vein occlusion. Injections were given at baseline and 4-month intervals, based on treatment assignment and study-defined re-treatment criteria. Because intravitreal SO was observed following injections in some participants, investigators were instructed, on September 22, 2006, to look for intravitreal SO at all study visits. On November 1, 2007, the luer cone syringe design replaced the staked-on syringe design.

RESULTS—464 participants received a total of 1205 injections between November 4, 2004 and February 28, 2009. Intravitreal SO was noted in 141/319 (44%) participants exposed only to staked-on syringes, 11/87 (13%) exposed to both syringe designs, and 0/58 exposed only to luer cone syringes ($p<0.0001$). Among participants with first injections after September 22, 2006, intravitreal SO was noted in 65/114 (57%) injected only with staked-on syringes compared with 0/58 injected only with luer cone syringes. Differential follow-up is unlikely to explain these results.

CONCLUSION—In the SCORE Study, luer cone syringe design is associated with a lower frequency of intravitreal SO droplet occurrence compared with the staked-on syringe design, likely due to increased residual space in the needle hub with the luer cone design.

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Introduction

Intravitreal silicone oil droplets have been reported following intravitreal injections of pegaptanib, bevacizumab, triamcinolone acetonide, and ranibizumab,[1,2] as well as in a participant who received intravitreal injections with amikacin, vancomycin, and triamcinolone acetonide.[1] None of the reported agents have silicone oil in their drug vehicle; the source of the silicone oil droplets is believed to be the syringe and/or needle used to deliver the drug. Dimethicone (polymethylsiloxane) is used as a lubricant for the syringe barrel, plunger, and needle. The silicone oil, which coats the inside of the syringe barrel and plunger, is employed to reduce friction between the syringe barrel and plunger so as to permit smooth movement of the plunger within the barrel. Silicone oil is also employed on the outside of the needle to reduce friction, permitting smooth movement of the needle through tissue.

Because intravitreal silicone oil droplets were reported in participants treated with intravitreal triamcinolone acetonide injection(s) by investigators in the **S**tandard Care versus **CO**rticosteroid in **RE**tinal Vein Occlusion (SCORE) Study (Figures 1A and 1B), the syringe design used in the SCORE Study was modified from a staked-on (Figure 2) to a luer cone (Figure 3) design in an attempt to decrease the frequency of intravitreal silicone oil occurrence. The rationale for syringe modification was that intravitreal silicone oil droplet formation was thought to result from “squeegeed” silicone oil from the inside of the syringe as the plunger was pushed through the barrel of the syringe. Modifying the syringe from a staked-on to a luer cone design created a 50 ul residual space in the needle hub, and it was hypothesized that this would decrease the frequency of intravitreal silicone oil droplets, since the “squeegeed” silicone oil would remain in the residual space rather than be injected into the vitreous cavity. The purpose of the current study is to evaluate the incidence of intravitreal silicone oil droplets associated with intravitreal injections using staked-on versus luer cone syringes in the SCORE Study.

Methods

The design and methods of the SCORE Study, which consists of two phase 3 multicenter randomized clinical trials conducted at 84 clinical sites in the United States, are described in detail elsewhere.[3–5] The 170 study investigators, all board-certified ophthalmologists with at least 1 year of retina fellowship training, enrolled 271 participants into the central retinal vein occlusion (CRVO) trial and 411 participants into the branch retinal vein occlusion (BRVO) trial. The eligible eye of each participant was randomized to one of three equally-sized parallel arms in either the CRVO trial or the BRVO trial; standard of care (SC), 1 mg intravitreal triamcinolone, and 4 mg intravitreal triamcinolone. Participants in the CRVO trial assigned to standard of care were observed. Participants in the BRVO trial assigned to standard care were treated with grid laser photocoagulation if a dense macular hemorrhage did not preclude treatment. If a dense hemorrhage was present, laser photocoagulation was postponed until clearing of the hemorrhage permitted laser treatment. Participants were treated with the randomly assigned treatment at baseline and at 4-month intervals, except when study-defined criteria to defer additional treatment or to employ the alternate treatment regimen were satisfied.

Between November 4, 2004 and October 31, 2007, all syringes used in the SCORE Study had a staked-on 27 gauge Becton Dickinson (Franklin Lakes, NJ) or Gerresheimer (Dusseldorf, Germany) needle. From November 1, 2007 until February 28, 2009, the SCORE Study used luer cone syringes (luer-slip design) with either a 30 gauge or a 27 gauge Becton Dickinson needle (the choice of needle size was at the discretion of each individual investigator). Both syringe types were made of glass. This report is based on 464 participants (1205 injections) who each had at least one study injection.

The SCORE Study investigators were first alerted to the issue of intravitreal silicone oil droplets in a memorandum from the Data Coordinating Center (The EMMES Corporation, Rockville, MD) on September 22, 2006. The droplets were presumed to be silicone oil due to their appearance and because of prior reports of this finding following intravitreal injection.[1,2] Investigators were instructed to specifically look for silicone oil droplets at each study visit (all participants underwent slit-lamp biomicroscopy and dilated funduscopic indirect ophthalmoscopy at each study visit) and to report the first date a silicone oil event was observed. All SCORE Study participants were informed of this issue through an addendum to their Informed Consent approved by each site's IRB.

When intravitreal silicone oil was observed (henceforth referred to as a "silicone oil event") in a participant by a SCORE Study physician, the date of the silicone oil event was imputed to be the date of the last injection prior to its report, although the event could actually have occurred at an earlier injection, and gone unnoticed by the investigator. Before the imputed date, the participant is said to be "at risk" for a silicone oil event. The time period a participant is at risk for a silicone oil event is measured by the number of injections, because it is presumed that silicone oil droplets result from the injection and do not spontaneously appear between injections. We also assume that the silicone oil event occurs at one specific time point. If, in reality, small increments of silicone oil are added by each injection, then we assume the event occurs when the cumulated oil increments surpass a threshold of clinical detectability.

Once a silicone oil event occurs, there is also a time period between that injection date and the date the silicone is reported. This reporting time is measured by the number of ophthalmic evaluation visits (either the Day 4 or Month 1 safety visits, regular 4-month evaluation, or supplemental visits) performed by the SCORE Study investigator since the last injection. The number of visits is used rather than calendar time because silicone oil cannot be reported between ophthalmic evaluation visits.

In the Results Section we report a simulation analysis designed to discover whether the absence of reported oil events in the luer cone cohort (Table 1, row 11; please see the Results section for an explanation of Table 1) could simply be due to inadequate time to report events that have occurred but have not yet been reported. In this analysis, we constructed a simulated luer cone cohort by randomly drawing with replacement from the staked-on syringe-only cohort after the warning date (Table 1, rows 7–8). More specifically, for each participant in the luer cone cohort, we randomly chose a replacement with the same number of injections from the staked-on cohort (note: participants with 4 injections with the luer cone syringe were allowed to "match" participants with 3 injections with the staked-on syringe, because there were no staked-on participants with 4 injections). We then aligned the enrollment date of the chosen participant from the staked-on cohort with that of the replaced participant from the luer cone cohort. Each newly simulated luer cone participant was assigned a score of 1 if a silicone oil event had occurred with an aligned reporting date before April 2, 2009 (the date of database closure) and was assigned a silicone oil score of 0 otherwise, i.e. if either there had been no silicone oil event, or there had been one, but the aligned report date was after the database closure date. This method of simulation embodies the "null hypothesis" of the simulation, namely that oil event rates and reporting rates were the same in the two cohorts, but there was less time to report after oil events in the luer cohort. After "substituting" all participants in the luer cone cohort, the summed simulated silicone oil scores were calculated to represent a typical number of silicone oil events expected to be reported in the luer cone cohort under the null hypothesis. We repeated the simulation 10,000 times.

For injection-specific silicone oil event probabilities reported in Table 3 and Table 4 (i.e., on a first injection, second injection, etc.), we assume that the probability that an event will occur to an individual is different at each injection. We supply Bayesian point estimates and 95%

credibility intervals for this probability assuming a binomial likelihood and a uniform prior. [Note: with this method, an observation of k successes in n trials leads to a point estimate of (k+1)/(n+2) for the probability, rather than the usual k/n.] Estimates assuming the probabilities are the same across injections and are derived in the same way, except the likelihood theory assumes that event waiting times follow a censored geometric distribution. Injections occurring after a reported silicone oil event are not part of the analysis.

Nineteen participants (31 injections) were excluded from the analysis because the participants had no ophthalmic evaluation visits on or after the warning date of September 22, 2006, and thus were never at risk for a reported oil event. Database closure for this report was April 1, 2009.

Results

Table 1 summarizes the history of intravitreal triamcinolone injections at risk for a silicone oil event, and the silicone oil droplet exposure of all SCORE Study participants who received such injections. Important to understanding changes in the risk of intravitreal silicone oil is the date the Data Coordinating Center first warned SCORE clinical centers about the possibility of intravitreal silicone oil (September 22, 2006) and the date of the switchover from the staked-on syringe to the luer cone syringes (October 31, 2007). Each row of Table 1 depicts a history of at-risk injections for a particular cohort relative to these dates, with the number of participants in the cohort specified in column 6. Rows in which column 4 is “Y” represent at-risk injections that culminated in a silicone oil event. Because investigators were instructed to report only the first silicone oil event for each participant, there is exactly one silicone oil event in Table 1 for each participant in such a row. Injections occurring after oil events are not shown. Rows in which column 4 is “N” depict all injections that did not terminate in an oil event. Numbers in column 10 represent the average of number of visits after the last injection in which the SCORE Study physician might have reported an oil event.

Row (1) of Table 1 represents 90 SCORE Study participants, all of whose 174 injections occurred before the warning date, and did not culminate in a silicone oil event. Column 10 shows that, on average, there were 5.6 visits after the last injection and also after the warning date in the cohort depicted in row (1), during which an already-alerted physician might have had an opportunity to observe and report intravitreal silicone oil (if it was there), but did not. Row (2) represents 26 participants, all of whose 61 injections occurred before the warning date and culminated in 26 silicone oil events. Column 10 shows that, on average, there were 2.5 visits that occurred after the last injection and also after the warning date, but at or before the time of the report of the silicone oil event (inclusive). That is, among the participants of row (2), there were 2.5 visits that were “at risk” for reporting a silicone oil event. Thus, column 10 depicts the time from injection to report in cases with an oil event, but time from injection to participant termination/database closure in cases without an oil event. When there are oil events, column 10 gives an idea of the shortest possible waiting times from event to report; these waiting times could in reality have been longer, because the oil events might actually have happened before their imputed event dates. When there are no reported oil events, a greater number in column 10 makes the absence of oil events more credible. Other rows in Table 1 are interpreted similarly.

For cohorts of participants depicted in Table 1 whose last injection culminated in a silicone oil event, there were an average of 1.9 to 3.0 subsequent visits necessary to identify the intravitreal silicone oil. For participants without a silicone oil event, “Mean Post-Injection Visits” ranged from 4.3 to 7.1 visits. As expected, “Mean Post Injection Visits” are more numerous when there are no oil events. There were 319 participants exposed only to the staked-on syringes (Table 1: Rows 1–4,7, and 8). Intravitreal silicone oil was noted in 141 (44%) of these

participants. Intravitreal silicone oil droplets were noted in 11 (13%) of the 87 participants exposed to both the staked-on and luer cone syringes (Rows 5, 6, 9, and 10). In this cohort, exposed to both types of syringes, we cannot determine whether the intravitreal silicone oil came from injections before or after switchover to the new syringe, although the intravitreal silicone oil was reported after the switch date. None of the 58 participants who were exposed only to the luer cone syringes (Row 11) reported intravitreal silicone oil; there were 136 injections in these participants.

Table 2 reports p-values from log-rank tests comparing time until oil events between selected cohorts within selected strata. The log-rank test comparing 3 cohorts of participants (staked-on only, luer cone only, and exposure to both staked-on and luer cone syringe designs) was significant at $p<0.0001$, as were log-rank tests comparing “staked-on only” to either “luer cone only” or “both staked-on and luer cone”. The log-rank test comparing “both staked-on and luer cone syringe” to “luer cone only”, however, was not significant ($p=0.06$). This pattern of significant and non-significant results held for log-rank tests within the following strata: participants in the SCORE-BRVO trial only, participants in the SCORE CRVO trial only, 1 mg injections only, and 4 mg injections only.

With respect to the “warned, staked-only” cohort (Table 1, rows 7–8), the log-rank test revealed no significant difference in waiting times between disease groups ($p=0.70$), or 1 mg versus 4 mg treatment groups ($p=0.07$). Of the injections with the luer cone syringe design, the investigators chose the 27-gauge needle 54% of the time and the 30-gauge needle 46% of the time.

Table 3 summarizes the timing of oil events in the 114 participants who experienced all their injections after the warning date, but before the switch date, when the staked-on syringe was still in use (Table 1: Rows 7 and 8). Of these 114 participants, 46 experienced a silicone oil event after their first injection, so that, for these participants, the estimated probability of experiencing a silicone oil event is 46/114=0.41 (95% crediblity interval: 0.37, 0.50). An additional 30 of the 114 participants did not experience a silicone oil event, but had no further injections, so that only 38 participants were at risk for an oil event following a second injection. Of these, 16 experienced silicone oil events, leading to an estimated probability of 0.43 for the silicone oil event, given that the individual was still at risk (95% credibility interval: 0.37, 0.58). Of the 7 participants who had a third injection and therefore were at risk of a silicone oil event, 3 experienced a silicone oil event, leading to an estimated probability of 0.44 for the silicone oil event (95% credibility interval: 0.33, 0.76). Overall, 65 of the 114 participants originally at risk experienced an oil event, while 49 did not, leading to an estimated probability of experiencing an oil event equal to 0.41 (95% credibility interval: 0.38, 0.49) per injection.

In the cohort of participants receiving injection with only the luer cone syringes (Table 4), there were 58 participants at risk of a silicone oil event after the first injection, of which 15 did not have further injections. Forty-three participants had a second injection, and of these, another 26 participants had a third injection, of which 9 had a fourth injection. None of these participants were reported to have a silicone oil event. The 95% credibility interval for the probability of experiencing an oil event in this group is (0.00, 0.03). That is, the upper 95% credibility limit in the luer cone cohort is approximately 1/10 of the lower 95% credibility limit for the probability of experiencing a silicone oil event in the cohort of participants who experienced all their injections after the warning date, but before the switch date.

The foregoing analysis finds stark differences between two cohorts; although investigators had been instructed to look specifically for intravitreal silicone oil droplets in both cohorts, many oil events were observed in the staked-on syringe cohort, while the luer cone syringe cohort reported no events. However, the analysis omits consideration of time from event to reporting;

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