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Sustained Release Intravitreal Liquid Drug Delivery Using Triamcinolone Acetonide for Cystoid Macular Edema in Retinal Vein Occlusion

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Abstract

Purpose—To investigate side effects seen with this formulation and to search for evidence of effectiveness after a single intravitreal injection of IBI-20089 in eyes with cystoid macular edema (CME) secondary to retinal vein occlusion.

Design—Prospective phase 1 clinical trial

Participants—10 patients with chronic CME due to retinal vein occlusion

Methods—Patients received a single intravitreal injection of IBI-20089 using a sequential dose escalation schedule. Each cohort consisted of five patients who received the intravitreal injection of the sustained liquid drug delivery system containing either 6.9 mg (25 ul) triamcinolone acetonide (TA) (Cohort 1) or 13.8 mg (50 ul) TA (Cohort 2). At each study visit, best corrected visual acuity testing, slit lamp biomicroscopy, intraocular pressure (IOP) measurement, dilated ophthalmoscopy, fundus photography and optical coherence tomography (OCT) were performed. Patients also underwent laboratory testing and physical examinations to monitor for any systemic adverse events.

Main Outcome measures—OCT central subfield thickness, ocular and systemic adverse events

Results—In Cohort 1, mean baseline OCT central subfield thickness (CST) was 477 microns (μ) and decreased to 369 μ at day 1 ($p < 0.06$), 387 μ at day 30 ($p = 0.18$) and 251 μ at day 360 ($p = 0.46$). In Cohort 2, mean baseline OCT CST was 518 μ , and decreased to 404 μ at day 1 ($p = 0.134$), 289 μ at day 30 ($p = 0.003$), 207 μ at day 180 ($p = 0.004$) and 278 μ at day 360 ($p = 0.009$). Related adverse events included elevation of IOP in three patients; two due to neovascular glaucoma (not related to study drug) and one which required a glaucoma tube shunt.

Conclusion—A single intravitreal injection of IBI-20089 resulted in a controlled and sustained delivery of a TA. Side effects included elevated IOP in three eyes, two of which had neovascular glaucoma.

An increasing number of retinal diseases are being treated with pharmacologic agents delivered into the vitreous. The use of sustained drug delivery systems can decrease the number of intravitreal injections required and hence the number of injection associated adverse events. For eyes with macular edema in which chronic suppression of inflammatory cytokines is beneficial, a long release profile is desirable. In addition, the ability to inject a drug delivery system through a small gauge needle is more comfortable for the patient and can safely be performed in the office. To address the challenge of ophthalmic sustained-release drug delivery, the Verisome®™ drug delivery technology was created. It is a proprietary technology encompassing a wide variety of excipients including carbonates, tocopherols and citrate esters. Unique combinations of these excipients are combined with each specific active drug ingredient. The dose and duration of release is designed for the targeted clinical application. The resultant biodegradable formulation can be injected, delivering the drug in a controlled release manner. This sustained-release liquid drug delivery system can be formulated with small molecule compounds and large biologics, such as monoclonal antibodies. In this study, the system was formulated with triamcinolone acetonide (TA), IBI-20089, and was designed to deliver the TA for up to a year with a single intravitreal injection.

In published pharmacokinetic studies in rabbits, the half-life of intravitreally injected TA without a delivery system was 1.6 days with no drug detectable by high performance liquid chromatography (HPLC) at 21 days in five out of six eyes, although drug effects were clinically observable to a mean of 23.3 days¹. In another study, intravitreal TA was cleared faster from vitrectomized eyes as compared with non-vitrectomized eyes². In contrast, in a rabbit study of IBI-20089 in which the drug product was injected into the posterior segment, TA was released up to 360 days with relatively constant levels of release per day (Data on file with the Food and Drug Administration [FDA]). Based on the toxicology data, the FDA granted clearance for use of IBI-20089 intravitreally in humans.

The purpose of this Phase 1 human study was to investigate side effects seen with this formulation and to search for evidence of effectiveness after a single intravitreal injection of IBI-20089 in eyes with cystoid macular edema (CME) secondary to retinal vein occlusion.

Materials and methods

An investigation new drug (IND) number and approval for clinical investigation of this drug product were obtained from the Food and Drug Administration (FDA). Protocol review and approval of the informed consent form were obtained by the Institutional Review Boards at participating sites prior to initiation of the study. Written informed consent was obtained from all patients prior to determination of full eligibility and was conducted accordance with the Health Insurance Portability and Accountability Act and Declaration of Helsinki. The study is registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) at www.ANZCTR.org and the clinical trial accession number is ACTRN12608000603314 (Accessed March 12, 2008).

Patients were eligible for the study if they had cystoid macular edema (CME) due to retinal venous occlusive (RVO) disease or secondary to cataract surgery with visual acuity 20/40 to 20/200 and central subfield thickness greater than 250 microns on optical coherence tomography (OCT) imaging (Stratus OCT 3, Carl Zeiss Meditec, Dublin CA). The three study locations were two private practices in Northern California and the retina clinic at

University of Illinois at Chicago. Ocular exclusion criteria included a history of glaucoma, ocular hypertension, visually significant cataracts, diabetic retinopathy or other ocular disease that could result in decreased visual acuity within one year. Exclusion criteria included any systemic or ocular malignancy, visual acuity less than 5 feet /200 in the non-study eye, steroid treatment (intravitreal, oral or intravenous) for CME in study eye within 90 days, systemic or intravitreal anti-vascular endothelial growth factor (anti-VEGF) within 90 days, systemic use of immunomodulatory agents, retinal neovascularization, diabetes, human immunodeficiency virus (HIV) or any other systemic illness which could result in an increased risk of early death.

Patients were enrolled in the study via a dose escalation schedule. The first five patients were enrolled into the 6.9 mg TA in 25 μ l group (Cohort 1). The patients were monitored for any local or systemic adverse events. After 60 days without any safety signals noted, enrollment into the 13.8 mg TA in 50 μ l group (Cohort 2) was initiated. Patients were followed for 360 days. Follow-up was performed at 1 day, 1 week, 1 month, 2 months, 4 months, 6 months, 9 months and 12 months.

Protocol assessments included visual acuity, ocular examinations, laboratory blood tests, OCT and fundus photography. At each study visit, a certified technician assessed visual acuity using Early Treatment of Diabetic Retinopathy (ETDRS) protocol refractions and charts. Ocular examinations included slit lamp biomicroscopy, measurement of intraocular pressure (IOP), and dilated ophthalmoscopy. At baseline and monthly visits, a review of systems, physical examination (consisting of auscultation of the heart, lungs, abdomen; examination of neck, limbs) and determination of blood pressure and heart rate were performed. Blood samples were sent for measurement of electrolytes (sodium, potassium, chloride, bicarbonate, and calcium), renal and metabolic tests (blood urea nitrogen, creatinine, glomerular filtration rate, and glucose), and liver function tests (total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total protein, albumin) at baseline, one week, and 60 days post-treatment.

OCT central 1 mm retinal thickness subfield measurements (CST) and quantitative assessments were obtained and calculated using 6 fast, low density scans and the Macular Thickness Map analysis at each study visit to assess retinal thickness. The photographer selected the clearest OCT image during the OCT exam. In the event of multiple retinal thickness measurements, the principal investigator at each site selected the CST number judged to be most accurate. Color fundus photographs of the central macula including the optic nerve were obtained at screening or baseline, months 3, 6, 9 and 12.

The doses of drug were administered as single intravitreal injections. IBI-20089 was received for clinical use in pre-filled, sterile syringes. Antisepsis and anesthesia were achieved according to standard protocols which included, in brief, anesthesia with proparacaine drops followed by 4% lidocaine applied with cotton swabs, eyelid antisepsis with 10% povidone iodine, surface antisepsis with 5% povidone iodine, a sterile eyelid speculum, and gloves for the injecting physician and technician. A sterile 30 gauge needle was attached to the syringe and all air expressed from the syringe so that the drug fully filled the hub and needle. After placement of the eyelid speculum, calipers were used to mark the injection location 3.5mm from the limbus, and the drug system was injected at the marked site as a single continuous injection to form the drug spherule. A sterile cotton swab was applied to the conjunctival surface to displace the conjunctiva in case of vitreous wicking. After the eyelid speculum was removed, TonoPen intraocular pressure and counting fingers vision were assessed. The pre-specified primary outcome was to assess the safety of the liquid drug delivery device as formulated with 6.9 mg and 13.8 mg of TA. The safety signals included ocular (endophthalmitis, uveitis, ocular hemorrhages, elevated IOP, retinal tears or

detachment) and systemic safety (alteration of blood chemistry or physical examination changes temporally related to the drug) signals. Pre-specified secondary outcomes were systemic safety of IBI-20089, change in macular edema as measured by OCT 1 mm CST and change in vision as measured by ETDRS (4 meters) protocol refraction and charts at each post-treatment time point.

Since this was a small phase one study, the data analysis was planned to be descriptive with no statistical hypothesis testing. Comparison of post-treatment OCT CST to baseline OCT CST measurements were performed. Missing data points utilized last observation carried forward.

Results

Between October 2007 and March 2009, potential patients were screened and 10 patients, nine of whom were women, were enrolled into the study at three study locations. Reasons for failures to enroll included a history of HIV infection, concomitant diabetic retinopathy, pre-existing glaucoma or patient declination of the study drug. Of the enrolled patients, four patients had branch retinal vein occlusions (BRVO) and six had central retinal vein occlusions (CRVO). The patient age range was from 55 to 88 years old. Duration of CME ranged from two to 26 months (median 8.5 months). Mean baseline visual acuity was 58.5 letters and ranged from 5 to 79 letters (20/ 800 to 20/25 [one patient]). The 20/25 patient was noted as a protocol violation as the baseline visual acuity was better than 20/ 40. This patient was allowed to remain in the study as the drug was already injected at the time of the discovery of the protocol violation). Mean central subfield thickness (CST) for Cohort 1 was 499 microns (μ), ranging from 299 μ to 635 μ . Mean CST for Cohort 2 was 518 μ , ranging from 349 μ to 673 μ .

Overall, OCT thickness decreased after treatment (Figure 1, 2). For the 6.9 mg cohort, mean OCT CST decreased from 477 μ at baseline to 369 μ at day 1 ($p < 0.06$), 387 μ at day 30 ($p = 0.18$), 301 μ at day 180 ($p = 0.18$), 244 μ ($p = 0.47$) day 270 and 251 μ ($p = 0.46$) at day 360. For the 13.8 mg cohort, mean OCT CST decreased from 518 μ at baseline to 404 μ at day 1 ($p = 0.134$), 289 μ at day 30 ($p = 0.003$), 207 μ at day 180 ($p = 0.004$), 276 μ ($p = 0.001$) at day 270 and 278 μ ($p = 0.009$) at day 360.

The patients showed a substantial drop in OCT CST as early as one week following therapy in both cohorts. In Cohort 1, there was one patient that showed a quantitative increase in the OCT CST despite the 20089 drug injection. In Cohort 2, there was a statistically significant decline in the OCT CST by week one.

At one year follow up, two of the patients in Cohort 1 had a recurrence of macular edema as reflected by increased retinal thickness. In contrast, all patients in Cohort 2 had sustained reductions in OCT CST at one year. One patient in Cohort 1 received an intravitreal dose of TA at day 161. This was the same (and only) patient who had an increase of the OCT CST seen on the OCT shortly after the injection of the study drug. No other patient received any additional steroid treatment.

No complications occurred during the actual injection of the drug. The drug delivery system appeared as a translucent sphere in the inferior vitreous base that shrank in size over time. Patients did not complain of a visual field defect and tolerated the presence of the drug gel sphere well. There were no complaints of photopsias or visual field changes. Ocular adverse events included conjunctival hemorrhage at the injection site in four patients and elevation of IOP in three patients. Two patients were noted to have vitreous hemorrhages at the injection site. The hemorrhage resolved spontaneously in both cases and did not limit visual

acuity. There were no cases of endophthalmitis, uveitis, lens injury, retinal tear or detachment in either cohort.

Two of the patients with elevated IOP had developed neovascular glaucoma from their CRVO during the duration of the study. Ischemic CRVO patients were not excluded from this phase 1 study. One neovascular glaucoma patient had an elevated IOP of 39 mmHg at the day 180 visit. She responded to topical IOP lowering drops and panretinal photocoagulation. At one year, she had a normal IOP and was off topical drops. The other neovascular glaucoma patient was noted to have an IOP of 31 mmHg at day 182. She underwent an anti-VEGF injection with resolution of the neovascularization and the IOP elevation. The third patient with elevated IOP was observed to have an elevated IOP at the day 60 visit and was prescribed topical medication. At day 245, examination revealed an IOP of 46 mmHg. A glaucoma consult resulted in the recommendation for filtration surgery. The subject underwent an Ahmed shunt at day 250 and IOP post-operatively returned to normal range.

One patient in Cohort 1 was noted to have a cataract at nine months after the injection. This cataract was noted to be possibly related to the study drug. No patients were noted to have progression of a cataract or development of a cataract in Cohort 2.

There were no associated laboratory abnormalities or systemic physical findings attributed to the study drug. No related systemic adverse events were found. There were three serious systemic adverse events, but all were judged by the investigators to be unrelated. One patient died of an unrelated systemic infection sustained during a fall and died prior to the day 270 visit. Another patient suffered a hip fracture (slipped on outdoor ice during the winter) and recovered fully. Another patient with chronic atrial fibrillation required atrioventricular nodal ablation and pacemaker placement during this study interval.

Case examples

Case 1 BRVO patient with two years of macular edema

A 55 y/o Hispanic-American woman had sustained a BRVO 26 months previously and had a visual acuity of 20/200. Her pretreatment OCT CST was 349 μ . She received the 13.8 mg dose of study drug in Cohort 2. Her pre-treatment fundus images are shown on Figures 3 a - c. A photo of the drug within this eye is shown on Figure 3 d. One month after the injection, her OCT CST had decreased to 208 μ and her visual acuity improved to 20/125 (Figure 3e). By 2 months, the cystic changes were mostly resolved and the OCT CST had decreased to 154 μ (Figure 3f). By six months, OCT CST was 125 μ and visual acuity was 20/ 80 (Figure 3g). By twelve months, OCT CST was 131 μ and visual acuity was 20/100 (PAM 20/ 80) (Figure 3h-i).

Case 2 CRVO patient with macular edema and development of neovascular glaucoma

A 74 y/o Caucasian woman had sustained a CRVO nine months previously. Her visual acuity was limited to 20/100 due to CME. A pretreatment OCT showed the CST was 622 μ (Figure 4 a-c). One month after treatment with the 13.8 mg dose of study drug, OCT CST was reduced to 473 μ and visual acuity was 20/63 (Figure 4d). Two months post-treatment, OCT CST was decreased to 261 μ and visual acuity was 20/80. By six months post-treatment, the OCT CST was 295 μ and visual acuity was 20/125 (Figure 4e). At that visit, it was noted that she had developed neovascularization of the iris and neovascular glaucoma and she received immediate panretinal photocoagulation (PRP). She responded well to the PRP with complete resolution of the neovascularization of the iris. She was prescribed topical timolol 0.5 % drops twice daily. Her IOP normalized. At nine months post-treatment, OCT CST was 457 μ and visual acuity was 20/200. She had recurrent CME, which was felt

to be related to the PRP. At twelve months, the OCT CST was 507 μ and her visual acuity was 20/160 (Figure 4 f, g). Nine months following her last study visit her intraocular pressure remains normal and there is no neovascularization of the iris or retina.

Discussion

This phase I study demonstrated preliminary evidence of sustained efficacy from a single intravitreal injection of IBI-20089 for cystoid macular edema (CME) secondary to RVO. No systemic adverse events were observed related to the injection procedure or drug delivery system. Although there were three cases of elevated IOP, two were associated with neovascular glaucoma related to the CRVO and not attributed to the drug delivery system. There was one case of presumed drug-related elevation of IOP and one case of progression of cataract. Evidence of bioactivity of the drug system was demonstrated by the rapid and sustained reduction in CST as measured with OCT.

Recent clinical trials have shown intraocular steroids to be efficacious in the treatment of macular edema for eyes with retinal vein occlusions. In the CRVO arm of the Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) Study, intravitreal injection of TA was shown to be better than observation.³ Intravitreal injections of TA were given every four months as needed. At one year, TA treatment resulted in a gain of 15 letters of visual acuity in 27 % of the 1 mg TA treated group (n=92), 26 % in the 4 mg TA group (n=91) versus 17 % of the untreated control eyes. Complications included elevation of intraocular pressure (IOP) by 10 or more mmHg in 16% in the 1 mg group and 26 % in the 4 mg group versus 2 % of observed eyes. There was also lens progression seen in 26 % of 1 mg group eyes and 33 % of 4 mg group eyes versus 18 % of observed eyes.

Recently the Ozurdex^{TM} implant was approved for sustained delivery of dexamethasone for CME in eyes with retinal vein occlusion. The study showed a faster time to reach a three-line improvement in visual acuity in the Ozurdex-treated eyes versus the sham eyes. However, the effect peaked at 60 to 90 days following the injection of the drug implant. Reinjection at six months was beneficial in some eyes. Ozurdex^{TM} resulted in improved visual acuity at 90 days but results were not sustained with one treatment at one year.⁴ The longer sustained effect (up to one year with the 13.8 mg dose) seen with IBI-20089, if proven in a larger study, would benefit these patients because of the reduction in the number of injections and the attendant potential complications. In the future, further work will be required to determine whether IBI-20089 can indeed result in sustained efficacy as compared to recently approved sustained drug delivery systems such as Ozurdex^{TM}.

This study showed biological early evidence of effectiveness of IBI-20089 to deliver TA over a long duration of time. A dose response effect was seen with the higher dose cohort showing a longer suppression of cysts and thickening of the retina as compared with baseline OCT measurements.

Limitations of this Phase 1 study include the inherent challenges of interpreting data from a small sample size, the inaccuracy of the Stratus OCT 3 software to measure extreme levels of macular edema, absence of a protocol fluorescein angiography to assess ischemia and a protocol deviation in which a subject with 20/25 vision was enrolled. In addition, there was not an independent reading center for this open label study.

In conclusion, we found that this liquid drug delivery system technology, with a single intravitreal injection, could result in a controlled and sustained delivery of a drug, in this case TA. We did note elevated IOP in three eyes. Two cases if elevated IOP were attributed to development of neovascular glaucoma and one was attributed to the drug. Other compounds can be delivered with this system. In particular, anti-VEGF drugs may be of

value for treatment of these eyes as VEGF has been associated with macular edema in eyes with retinal vein occlusion.⁵ The recent “A Study of the Efficacy and Safety of Ranibizumab Injection in Patients With Macular Edema Secondary to Branch Retinal Vein Occlusion (BRAVO)” and “A Study of the Efficacy and Safety of Ranibizumab Injection in Patients With Macular Edema Secondary to Central Retinal Vein Occlusion (CRUISE)”^{6,7} clinical trial results suggest that repeated anti-VEGF therapy in these eyes is efficacious for improving visual acuity and reducing macular edema. Further work using this technology formulated with such drugs would be of interest.

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References

1. Scholes GN, O'Brien WJ, Abrams GW, Kubicek MF. Clearance of triamcinolone from vitreous. *Arch Ophthalmol*. 1985; 103:1567–9. [PubMed: 4051860]
2. Chin HS, Park TS, Moon YS, Oh JH. Difference in clearance of intravitreal triamcinolone acetonide between vitrectomized and nonvitrectomized eyes. *Retina*. 2005; 25:556–60. [PubMed: 16077349]
3. SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. *Arch Ophthalmol*. 2009; 127:1101–14. [PubMed: 19752419]
4. Haller JA, Bandello F, Belfort R Jr, et al. OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology*. 2010; 117:1134–46. [PubMed: 20417567]
5. Campochiaro PA, Hafiz G, Shah SM, et al. Ranibizumab for macular edema due to retinal vein occlusions: implication of VEGF as a critical stimulator. *Mol Ther*. 2008; 16:791–9. [PubMed: 18362932]
6. Campochiaro PA, Heier JS, Feiner L, et al. BRAVO Investigators. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary endpoint results of a phase III study. *Ophthalmology*. 2010; 117:1102–12. [PubMed: 20398941]
7. Brown DM, Campochiaro PA, Singh RP, et al. CRUISE Investigators. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology*. 2010; 117:1124–33. [PubMed: 20381871]

Figure 1.
Graph of optical coherence tomography central subfield thickness measurements over time for each patient in the 6.9 mg dose cohort.

Figure 2.
Graph of optical coherence tomography central subfield thickness measurements over time for each patient in the 13.8 mg dose cohort.

Figure 3.

Fundus and optical coherence tomography images of patient case 1. Note the resolution of the cystoid macular edema (CME) with treatment. a. (top row upper left photo) Pretreatment fundus photos shows dilation and tortuosity of the superior branch retinal vein and presence of macular lipid. b (top row middle photo) There is a dense deposit of foveal lipid and adjacent circinate rings prior to treatment. c. (top row right image) Pretreatment optical coherence tomography shows the marked cystic edema within the outer retinal layers involving the foveal area and extending temporally; the central subfield thickness was 349 μ . d. (middle row left photo) Slit lamp photo through the pupil shows the appearance of the drug ball one week post-injection in the inferotemporal periphery. The Verisome is a milky semi-opaque ball with a linear extension. The linear extension (resulting from expression of the last amounts of piqued drug from syringe during injection) coalesced over the next month into the drug ball. e. (middle row middle image) optical coherence tomography at one month after the injection shows resolution of the foveal edema. The central subfield thickness had decreased to 208 μ and there is some outer retinal edema temporally. f. (middle row right image) optical coherence tomography at two months shows almost complete resolution of the cystic changes temporally; central subfield thickness was 154 microns. g. (bottom row left image) optical coherence tomography at six months shows maintained resolution of the edema; central subfield thickness was 125 μ . h. (bottom row middle image) optical coherence tomography at 12 months shows no CME; central subfield thickness was 131 μ . i. (bottom row right photo) Corresponding fundus photo at 12 months

shows remaining foveal lipid with resolution of the lipid in the papillomacular bundle region.

Figure 4.

Fundus and optical coherence tomography images of patient case 1. Note the resolution of the cystoid macular edema (CME) with treatment. a. (top row left photo) Pretreatment fundus photos shows dilation and tortuosity of the branches of the central retinal vein with associated nerve fiber layer and blot hemorrhages. There is optic disc edema. b. (top row middle photo) Pretreatment macular fundus photo shows the presence of retinal blot, nerve fiber layer and dot hemorrhages. c. (top row right image) Pretreatment optical coherence tomography shows marked cystic edema involving the foveal area; the central subfield thickness was 673 μ . d. (middle row left image) optical coherence tomography at one month after the injection shows some resolution of the outer retinal edema. The central subfield thickness had decreased to 473 μ . e. (middle row middle image) optical coherence tomography at six months shows marked reduction of the large areas of CME with only a few central cysts in the foveal area; central subfield thickness was 295 μ . f. (middle row right image) optical coherence tomography at 12 months shows some recurrent CME following panretinal photocoagulation for neovascular glaucoma; central subfield thickness was 507 μ . g. (bottom photo) Corresponding fundus photo at 12 months shows shunt vessels at the disc but absence of disc neovascularization. Note the central foveal cyst and rare hemorrhages.