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

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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: Ten patients with chronic CME resulting from retinal vein occlusion.

Methods: Patients received a single intravitreal injection of IBI-20089 using a sequential dose escalation schedule. Each cohort consisted of 5 patients who received the intravitreal injection of the sustained liquid drug delivery system containing either 6.9 mg (25 μl) triamcinolone acetonide (TA; cohort 1) or 13.8 mg (50 μl) TA (cohort 2). At each study visit, best-corrected visual acuity testing, slit-lamp biomicroscopy, 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: Optical coherence tomography central subfield thickness, ocular and systemic adverse events.

Results: In cohort 1, mean baseline OCT central subfield thickness (CST) was 477 μm and decreased to 369 μm at day 1 ($P<0.06$), 387 μm at day 30 ($P = 0.18$), and 251 μm at day 360 ($P = 0.46$). In cohort 2, mean baseline OCT CST was 518 μm and decreased to 404 μm at day 1 ($P = 0.134$), 289 μm at day 30 ($P = 0.003$), 207 μm at day180 ($P = 0.004$), and 278 μm at day 360 ($P = 0.009$). Related adverse events included elevation of IOP in 3 patients, in 2 because of neovascular glaucoma (not related to study drug) and in 1 who required a glaucoma tube shunt.

Conclusions: A single intravitreal injection of IBI-20089 resulted in a controlled and sustained delivery of a TA. Side effects included elevated IOP in 3 eyes, 2 of which had neovascular glaucoma.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2011;118:1416–1422

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 be performed safely in the office. To address the challenge of ophthalmic sustained-release drug delivery, the Verisome drug delivery technology (Icon Bioscience, Sunnyvale, CA) 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 1 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 5 out of 6 eyes, although drug effects were clinically observable to a mean of 23.3 days.[1] In another study, intravitreal TA was cleared faster from vitrectomized eyes as compared with non-vitrectomized eyes.[2] 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). Based on the toxicology data, the Food and Drug Administration granted clearance for use of IBI-20089 intravitreally in humans.

ISSN 0161-6420/11/$–see front matter
doi:10.1016/j.ophtha.2010.12.029

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.

Patients and Methods

An investigational new drug number and approval for clinical investigation of this drug product were obtained from the Food and Drug Administration. Protocol review and approval of the informed consent form were obtained by the institutional review boards at participating sites before initiation of the study. Written informed consent was obtained from all patients before determination of full eligibility and was conducted in accordance with the Health Insurance Portability and Accountability Act and the Declaration of Helsinki. The study is registered with the Australian New Zealand Clinical Trials Registry 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 CME resulting from retinal venous occlusive disease or secondary to cataract surgery with visual acuity 20/40 to 20/200 and central subfield thickness of more than 250 μm on optical coherence tomography (OCT) imaging (Stratus OCT 3; Carl Zeiss Meditec, Dublin, CA). The 3 study locations were 2 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 1 year. Exclusion criteria included any systemic or ocular malignancy, visual acuity less than 5 feet/200 in the nonstudy eye, steroid treatment (intravitreal, oral, or intravenous) for CME in the study eye within 90 days, systemic or intravitreal anti–vascular endothelial growth factor (VEGF) treatment within 90 days, systemic use of immunomodulatory agents, retinal neovascularization, diabetes, human immunodeficiency virus or any other systemic illness that could result in an increased risk of early death.

Patients were enrolled in the study via a dose-escalation schedule. The first 5 patients were enrolled into the 6.9 mg TA in 25 μl 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 μl group (cohort 2) was initiated. Patients were followed up 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 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 and examination of the neck and 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 and at 1 week and 60 days after treatment.

The OCT central 1-mm retinal central subfield thickness (CST) measurements 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 examination. 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 and at months 3, 6, 9, and 12.

The doses of drug were administered as single intravitreal injections. IBI-20089 was received for clinical use in prefilled, sterile syringes. Antisepsis and anesthesia were achieved according to standard protocols that 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 was 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 3.5 mm 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, the Tono-Pen IOP (Reichert Technologies, Buffalo, NY) and counting fingers visual acuity were assessed. The prespecified primary outcome was to assess the safety of the liquid drug delivery device as formulated with 6.9 mg and 13.8 mg TA. The safety signals included ocular (endophthalmitis, uveitis, ocular hemorrhages, elevated IOP, and retinal tears or detachment) and systemic safety (alteration of blood chemistry or physical examination changes temporally related to the drug) signals. Prespecified 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 Early Treatment of Diabetic Retinopathy (4 m) protocol refraction and charts at each posttreatment time point.

Because this was a small phase 1 study, the data analysis was planned to be descriptive with no statistical hypothesis testing. Comparison of posttreatment OCT CST with baseline OCT CST measurements were performed. Missing data points used last observation carried forward.

Results

Between October 2007 and March 2009, potential patients were screened and 10 patients, 9 of whom were women, were enrolled into the study at 3 study locations. Reasons for failures to enroll included a history of human immunodeficiency virus infection, concomitant diabetic retinopathy, pre-existing glaucoma, or patient declination of the study drug. Of the enrolled patients, 4 patients had branch retinal vein occlusion and six had central retinal vein occlusion (CRVO). The patient age range was 55 to 88 years. Duration of CME ranged from 2 to 26 months (median, 8.5 months). Mean baseline visual acuity was 58.5 letters and ranged from 5 to 79 letters (Snellen equivalent, 20/800–20/25 [1 patient]). The 20/25 patient was noted as a protocol violation because 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 CST for cohort 1 was 499 μm, ranging from 299 to 635 μm. Mean CST for cohort 2 was 518 μm, ranging from 349 to 673 μm.

Overall, OCT thickness decreased after treatment (Figs 1 and 2). For the 6.9-mg cohort, mean OCT CST decreased from 477 μm at baseline to 369 μm at day 1 ($P<0.06$), 387 μm at day 30 ($P = 0.18$), 301 μm at day 180 ($P = 0.18$), 244 μm ($P = 0.47$) day 270, and 251