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Dexamethasone Intracameral Drug-Delivery Suspension for Inflammation Associated with Cataract Surgery

A Randomized, Placebo-Controlled, Phase III Trial

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Purpose: To evaluate the safety and efficacy of an anterior chamber intracameral dexamethasone drug-delivery suspension (IBI-10090; DEXYCU; Icon Bioscience Inc., Newark, CA) that provides medication for up to 21 days with a single application in treating postoperative inflammation in patients undergoing cataract surgery.

Design: Prospective, randomized, double-masked, multicenter trial.

Participants: Patients with preoperative best-corrected visual acuity of 20/30 to 20/200 undergoing unilateral cataract surgery by phacoemulsification were randomized to receive IBI-10090 or placebo.

Methods: Three hundred ninety-four patients were randomized 1:2:2 to receive 5-μl injections of placebo or 5-μl injections of 342 or 517 μg IBI-10090 dexamethasone drug delivery suspension injected into the anterior chamber at the conclusion of cataract surgery. Patients were followed for 90 days after surgery.

Main Outcome Measures: Primary outcome was anterior chamber cell (ACC) clearing (ACC score of 0) in the study eye at postoperative day (POD) 8. Secondary outcome measures were anterior chamber flare and ACC plus flare clearing in the study eye. Ocular and nonocular adverse events were assessed.

Results: Anterior chamber cell clearing at POD 8 was achieved in 25.0% of eyes in the placebo group and in 63.1% and 66.0% of eyes in the 342- and 517-μg treatment groups, respectively ($P < 0.001$). Anterior chamber flare clearing at POD 8 was achieved by 63.8% of eyes in the placebo group and in 92.4% and 89.1% of eyes in the 342- and 517-μg IBI-10090 treatment groups, respectively ($P < 0.001$). Anterior chamber cell plus flare clearing at POD 8 was achieved in 33.8% of eyes receiving placebo and in 63.1% and 67.3% of eyes receiving 342- and 517-μg IBI-10090, respectively ($P < 0.001$). Adverse events among the 3 groups were similar, and no serious ocular adverse events were reported up to POD 90.

Conclusions: The IBI-10090 dexamethasone drug-delivery suspension placed in the anterior chamber after cataract surgery at concentrations of 342 and 517 μg was safe and effective in treating inflammation occurring after cataract surgery and may be an alternative to corticosteroid drop installation in this patient population. *Ophthalmology 2018;■:1–8 © 2018 by the American Academy of Ophthalmology*

Cataract is the leading cause of blindness in the world.[1] In the United States alone, cataract affects 20.5 million (17.2%) Americans older than 40 years[2]; by 80 years of age, its prevalence increases to 1 in every 2 Americans. By 2020, the number of Americans with cataract is estimated to increase to 30.1 million, or nearly 10% of the United States population.[3] In 2017, it is estimated that 4 million surgeries will be performed on a yearly basis. Most patients (>99.5%) undergoing routine phacoemulsification cataract surgery do not experience serious vision-threatening post-surgical complications. However, each year in the United States, 150 000 complications occur, reported in approximately 5% of patients.[4] During phacoemulsification cataract surgery, unavoidable tissue damage can trigger an ocular inflammatory response[5] that can induce intraocular vasodilation and increase vascular permeability. This can disrupt and break down the blood–ocular barrier, increasing anterior chamber cells and flare. As a result, patients can experience pain and discomfort as well as impaired vision. After cataract surgery, inflammation remains a leading cause of patient discomfort, delayed recovery, and reduced visual outcomes.[6,7] Preventing such complications and effectively managing ophthalmic inflammation after surgery is vital in preventing complications. Immediate postsurgical treatment also can preclude more serious complications such as cystoid macular edema, the most common vision-threatening complication of cataract surgery.

To reduce such inflammation risk, ophthalmologists commonly use a prophylactic perioperative regimen consisting of topical corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs). The only Food and Drug

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Administration–approved topical corticosteroid formulations (difluprednate 0.05% and rimexolone 1%) are administered as ocular drops 4 times daily for 14 days or more.[8,9] Topical dexamethasone sodium 0.1% and prednisone acetate 1% also are used commonly off label with the same dosing schedule[10] for managing inflammation. Nonsteroidal anti-inflammatory drug eye drops have become a mainstay of managing ocular pain and inflammation[5] and include ketorolac tromethamine 4 times daily, diclofenac 4 times daily, bromfenac once and twice daily, and nepafenac once and thrice daily, all of which have been approved for treating postoperative inflammation. Treatment may be more effective when corticosteroids and NSAIDs are used in combination, as demonstrated by Cable,[11] who used both bromfenac and nepafenac after cataract surgery.

However, patient compliance and other problems involving administration with elderly patients self-administering medication drops can vary widely.[12] In a study of patients treated for glaucoma or ocular hypertension, Schwartz et al[13] found that 42% have difficulty administering medication drops and 18% touch the eye or conjunctiva. In another study, 11% of patients older than 80 years failed to deliver drops to the conjunctival pouch and 61% scratched the cornea or conjunctiva with the applicator.[14] Adherence to prescribed treatment after cataract surgery has not been assessed fully, but in general, adherence decreases with the number of daily doses. Many patients have mental or physical disabilities that limit their ability to deliver topical eye drops appropriately. Clearly, a more effective method for delivering effective and safe medications to the eye after cataract surgery is needed.

IBI-10090 (DEXYCU; Icon Bioscience Inc., Newark, CA) is a novel, bioabsorbable drug-delivery system for anterior chamber intracameral placement of dexamethasone, which is being developed and studied for treating inflammation associated with cataract surgery. In animal models, therapeutic levels of IBI-10090 were maintained for up to 21 days after a single intracameral administration (Vernon Wong, MD, unpublished data, August 2010). In a phase II/III study, IBI-10090 was dosed at 513, 776, and 1046 μg in more than 170 patients undergoing phacoemulsification cataract surgery. At all 3 doses, IBI-10090 was found to be safe and effective, achieving anterior chamber clearing at postoperative day (POD) 8 and demonstrating favorable efficacy compared with commercially available topical treatments. To extend these findings in a controlled trial, we undertook a phase III randomized, double-masked, controlled, multicenter trial to evaluate the efficacy and safety of 2 concentrations of IBI-10090 versus placebo for reducing ocular inflammation in patients undergoing phacoemulsification cataract surgery.

Methods

Study Design

This trial was a 90-day randomized, placebo-controlled, double-masked, multicenter study (ClinicalTrials.gov identifier, NCT02006888) undertaken at 27 US investigator sites that enrolled 394 patients randomized to receive placebo or active treatment. The trial was designed to evaluate the efficacy and safety of a novel intracameral dexamethasone drug-delivery suspension (IBI-10090) for treating inflammation associated with cataract surgery. The study was conducted in accordance with Good Clinical Practice (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E6), applicable Food and Drug Administration regulations, and the Health Insurance Portability and Accountability Act. The study protocol was approved by an institutional review board at Schulman Associates before the start of the study, and all participants provided written informed consent.

The screening period covered up to 45 days. After written informed consent was obtained, eligible patients were assigned randomly in a 1:2:2 ratio to receive 5 μl of placebo or 342 or 517 μg of dexamethasone drug-delivery suspension placed into the anterior chamber after completion of cataract surgery. One eye was chosen as the study eye for each patient. All study site personnel, the designated physicians, the patients, and the sponsor and its agents were masked to treatment drug dose assignment. Only the randomization provider had access to the unmasking code.

During the 90-day study duration, patient visits were scheduled on day 0 (baseline) and on PODs 1, 3, 8, 14, 30, and 90 to evaluate safety and efficacy. Patients received their masked assigned treatment on day 0, the day of phacoemulsification cataract surgery. The primary efficacy end point was evaluated at POD 8.

Patients

Male or female patients 40 years of age or older scheduled for unilateral cataract surgery by phacoemulsification with posterior chamber intraocular lens implantation were considered for inclusion in this trial.

Patient Inclusion Criteria

Patient had to provide written informed consent by signing the informed consent approved by the institutional review board. The patients had to demonstrate best-corrected visual acuity of 20/30 to 20/200 (with glare testing, if necessary) in the study eye and better than 20/200 in the fellow eye. Patients considered by the investigator had to have a visual acuity potential better than 20/30 in the study eye. Patients had to have a corneal endothelial cell count by specular microscopy in the study eye of at least 2000 cells/mm^2 with normal cell morphologic features. Women of childbearing potential (premenopausal by medical history) had to demonstrate negative pregnancy test results on day 0 and be using an effective method of birth control from screening for the duration of the study.

Patient Exclusion Criteria

Exclusion criteria included the following: use of any ocular, topical, or oral corticosteroids within 7 days before day 0; receipt of a periocular corticosteroid injection in the study eye in the 3 months before screening; receipt of any intravitreal corticosteroid delivery vehicle (e.g., Retisert [Bausch & Lomb Incorporated, Bridgewater, NJ], Ozurdex [Allergan, Inc., Irvine, CA], Iluvien [Alimera Sciences, Inc., Alpharetta, GA]) in the study eye at any time; requiring treatment with any corticosteroids by any route, except inhalation, during the study; allergy or hypersensitivity to dexamethasone; a known response to steroids (corticosteroid-related intraocular pressure [IOP] elevation in either eye); use of topical ocular NSAIDs in the study eye within 15 days before day 0; prior intraocular (nonlaser) surgery in the study eye within 6 months before screening; prior intraocular laser surgery in the study eye within 3 months before screening; and any planned intraocular or laser surgery in the study eye for the duration of the study.