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FROM SAN FRANCISCO:

Management of Post-Surgical Ocular Pain and Inflammation
This continuing medical education activity is provided by VINDICO medical education
This activity is supported by an educational grant from Ocular Therapeutix, Inc.
Drug Delivery:
The Unmet Need The Five Cs

- Compliance
- Cornea
  - Dry eye
- Comfort
- Cost
- Cosmesis
  - Red eye
• 31% of patients undergoing cataract surgery stated they had difficulty inserting drops and 92% of patients used improper techniques for drop instillation.
Dexamethasone Suspension for Intraocular Administration

• A novel, bioabsorbable drug delivery product for anterior chamber intracameral placement of DEX

• Therapeutic levels are maintained for up to 21 days with a single administration

DEX = dexamethasone.
Dexamethasone Intracameral Drug-Delivery Suspension for Inflammation Associated with Cataract Surgery
A Randomized, Placebo-Controlled, Phase III Trial

Eric Donnenfeld, MD, 1 Edward Holland, MD 2

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 mg injections of placebo or 5 mg injections of 342 or 517 mg 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-mg IBI-10090 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-mg 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-mg 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 mg 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;125:799-806 * 2018 by the American Academy of Ophthalmology

The last observation carried forward (LOCF) method was used to impute missing data and treatment failure was assumed if a patient received rescue medication.
Safety of IBI-10090 for inflammation associated with cataract surgery: Phase 3 multicenter study

Eric D. Donnenfeld, MD, Kerry D. Solomon, MD, Cynthia Matossian, MD

**Purpose:** To compare the safety and efficacy of IBI-10090 anterior chamber intracameral dexamethasone drug-delivery suspension (Dexycu) with those of prednisolone acetate 1.0% ophthalmic drops in treating inflammation after cataract surgery.

**Setting:** Eleven centers in the United States.

**Design:** Prospective randomized open-label multicenter trial.

**Methods:** Patients were randomized 2:1 to receive a 5 μl injection of 517 μg IBI-10090 in the anterior eye chamber or topical prednisolone 1.0% drops (1 drop 4 times daily for 3 weeks). The postoperative follow-up was 90 days. The primary outcome was safety, evaluated by the incidence and severity of adverse events. Exploratory measures were anterior chamber flare, anterior chamber cell, and anterior chamber cell-flare clearing.

**Results:** One hundred twenty-six IBI-10090 patients and 55 prednisolone patients were included in the safety analysis. Two serious adverse events unrelated to treatment were reported. The decrease in endothelial cell density was not significantly different between groups. The most common adverse events were increased intraocular pressure (11.1%), iritis (6.3%), and systemic (7.9% IBI-10090 group; 10.9% prednisolone group). By 8 days postoperatively, 51.6% of IBI-10090 eyes and 50.9% of prednisolone eyes had anterior chamber cell clearing; more than 98% of eyes had clearing at 90 days. The anterior chamber flare and anterior chamber cell-flare clearing results were similar. Of IBI-10090 patients, 68.7% strongly agreed that not having to use eyedrops was very convenient; 39.2% using prednisolone 1.0% strongly stated they would have preferred dropless therapy.

**Conclusion:** The safety and efficacy of IBI-10090 and prednisolone 1.0% were similar, with IBI-10090 preferred over drops.
Patients With ACC Grade 0 at Day 8 Sustained Release DEX Versus Prednisolone Acetate 1%

Sustained-release dexamethasone for the treatment of ocular inflammation and pain after cataract surgery

Thomas Walters, MD, Michael Endl, MD, Thomas R. Elmer, MD, Jeffrey Levenson, MD, Parag Majmudar, MD, Samuel Masket, MD

**PURPOSE:** To evaluate the safety and efficacy of dexamethasone as a sustained-release drug depot when placed in the canaliculus for the treatment of ocular inflammation and pain in cataract surgery patients.

**SETTING:** Four private practice sites in the United States.

**DESIGN:** Multicenter randomized double-masked clinical trial.

**METHODS:** Patients were randomized (1:1) to receive either the sustained-release dexamethasone or a placebo vehicle punctum plug inserted into the inferior distal canaliculus of the operated eye intraoperatively during cataract surgery. The primary endpoints were the proportions of patients with absence of cells or pain in the anterior chamber at 8 days. Secondary endpoints included cells, flare, pain, and the presence of the device at various timepoints through 30 days.

**RESULTS:** Approximately one fifth (20.7%) of patients in the sustained-release dexamethasone group had an absence of anterior chamber cells at 8 days compared with 10.0% in the placebo group (P = .1485). A higher proportion of patients in the sustained-release dexamethasone group (79.3%) than in the placebo group (30.0%) had an absence of ocular pain at 8 days (P < .0001) and at all other timepoints (P < .0002). There were significantly higher proportions of patients in the sustained-release dexamethasone group than in the placebo group with an absence of anterior chamber cells, anterior chamber flare, and pain at several timepoints through 30 days (P ≤ .0251).

**CONCLUSION:** Sustained-release dexamethasone provided elution of drug for up to 1 month after cataract surgery, providing clinically significant reductions in inflammation and pain.

**Financial Disclosure:** Dr. Masket is a consultant to and shareholder in Ocular Therapeutics, Inc. No other author has a financial or proprietary interest in any material or method mentioned.

Sustained-Release Dexamethasone

- Bioabsorbable intracanalicular hydrogel plug
- Drug delivery 1 month
Insertion & Visualization

Source: Dr. Eric Donnenfeld
Bilateral Cataract Surgery
Bilateral DEX Intracanalicular Insert

DEX = dexamethasone.
Source: Dr. Eric Donnenfeld
Dexamethasone Intracanalicular Insert Reduced Pain and Inflammation Following Cataract Surgery

Proportion of Patients Achieving the Primary Efficacy Endpoint

- Absence of Ocular Pain, Day 8: 79.6% (DEX) vs 52.3% (Placebo)
- Absence of AC Inflammation, Day 14: 61.3% (DEX) vs 31.2% (Placebo)

P < 0.0001 for both endpoints, ITT-LOCF

DEX = dexamethasone intracanalicular insert

Purpose: To evaluate the position of dexamethasone intracanalicular insert (DEX) in the canaliculus following cataract surgery.

Methods: Three prospective, multicenter, double-masked Phase 3 trials were conducted to evaluate the safety and efficacy of 0.4-mg dexamethasone hydrogel insert (DEX), and 541 patients were randomized to receive DEX. The number of DEX inserts retained in the canaliculus were captured during the 30-day postoperative period, along with the reason for removal and ease of removal.
Retention of DEX, a Sustained-Release Corticosteroid in Phase 3 Clinical Trial Program

• Results
  – Retention of DEX was 99.6% in the postoperative period, with need for removal in two subjects.
  – Removals were successfully performed by manually applying pressure and were rated easy or moderately easy to remove.
  – No inserts were removed for an adverse event.

• Conclusions
  – DEX was well retained throughout the postoperative 30-day period. While infrequent, removals were easy to moderately easy when necessary.

DEX = dexamethasone intracanalicular insert
Characterization and Management of Elevated IOP With an Intracanalicular Dexamethasone Insert After Cataract Surgery

**Purpose:** To characterize IOP change following cataract surgery in Phase 3 Intracanalicular Dexamethasone Insert (DEX) studies.

**Methods:** IOP measures from all visits in three Phase 3 trials (DEX/PV: N = 539/385) were captured and ≥10 mmHg over baseline were reported as IOP-related adverse events (AEs).
Characterization and Management of Elevated IOP With an Intracanalicular DEX Insert After Cataract Surgery

• Results
  – Mean IOP changes from baseline (DEX/PV-15.5/15.8 mmHg) were 1.7 mmHg (DEX) and 0 mmHg (PV) on Day 2 and ranged from −0.6 to −1.2 mmHg (DEX) and −1.4 to −2.2 mmHg (PV) from Days 4-30.
  – IOP change ≥10 mmHg from baseline was seen in 34 (DEX, 6.3%) versus 9 (PV, 2.3%) subjects on Day 2 and ranged from 2 to 3 (DEX, 0.4%-0.6%) versus 1 to 2 (0.3%-0.5%) from Days 4-30.
  – All reported IOP-related AEs were suspected to be surgery related and not DEX related.
  – Management involved no action taken (DEX/PV-15/3), medication therapy (17/8), and fluid released through paracentesis (12/4), and all final outcomes were recovered/resolved.

AEs = adverse events; IOP = intraocular pressure.
Conclusions

- Peak IOP elevation was on Day 2 and was attributable to surgery and not DEX related.
Differences in Postsurgical Pain and Inflammation Outcome of Patients Receiving DEX Insert Based on Fellow Eye Lens Status

• **Purpose:** To evaluate the difference in postoperative pain and inflammation in patients receiving DEX insert based on cataract surgery performed in the first versus second eye.

• **Methods:** 3 prospective, multicenter, double-masked Phase 3 trials were conducted, and results were integrated for analysis. Subjects were divided based on documented medical history of cataract extraction in the non-study eye.

Differences in Postsurgical Pain and Inflammation Outcome of Patients Receiving DEX Insert Based on Fellow Eye Lens Status

• Results:
  – 43.5% of patients (164/377) randomized to DEX and 49.8% of patients (128/257) randomized to placebo underwent a second eye cataract surgery.
  – In the DEX arm, absence of ocular pain at Day 8 was 80.5% and 76.2%, and absence of anterior chamber cells at Day 14 was 44.8% and 39.6%, after first and second surgeries, respectively.
  – In both cohorts, DEX was statistically significantly superior to placebo (P<.05 for all).

Differences in Postsurgical Pain and Inflammation Outcome of Patients Receiving DEX Insert Based on Fellow Eye Lens Status

- **Conclusion:** In patients receiving DEX, there was no observed difference in ocular pain or inflammation based on operative eye status.
Phenylephrine/ketorolac
Effect of Phenylephrine and Ketorolac Intracameral Solution 1%/0.3% on Pain and Opioid Usage During Cataract Surgery

• **Purpose:** To assess the impact of phenylephrine 1%/ketorolac 0.3% on opioid use during cataract surgery

• **Methods:**
  - 39 subjects were prospectively assigned to intracameral p/k (study group, N=27) or epinephrine (control arm, N=12).
  - All subjects received preoperative lidocaine topical gel and 0.5 cc intracameral PF lidocaine 1% at surgery start.
  - Subjects could request IV fentanyl analgesia during surgery if needed.
  - Primary outcomes were visual analog scale pain scores during surgery (scale of 0-10), measured 10 min post-op, and needed for IV fentanyl.

IV = intravenous.
Effect of Phenylephrine and Ketorolac Intracameral Solution 1%/0.3% on Pain and Opioid Usage During Cataract Surgery

• **Results:** Mean pain score was 2.31 ± 1.52 in the study group versus 4.76 ± 2.10 in the control arm (P<.0005). Two study group subjects (7.4%) requested IV analgesia versus four in the control arm (33.3%) (P=.04).

• **Conclusion:** In addition to published studies showing prevention of miosis and intraoperative floppy eye syndrome and reduced complications and pigment epithelial detachment use, administration of p/k reduced pain levels by >50%, and the need for opioids during cataract surgery by nearly 80%.

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Mucus Penetrating Particles (MPPs)
Loteprednol etabonate suspension
Mucus Penetrating Particles

- Surface engineered nanoparticles diffusing through mucus
- Nanoparticle core of crystalline drug
- Proprietary surface engineering made of GRAS polymers
- Safety of an ester steroid
- Significant intraocular penetration