Treatment Options for Ocular Inflammation

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Ester vs Ketone Corticosteroids

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Difluprednate 0.05% (Durezol)

- “There is increased bioavailability and dose uniformity resulting from the formulation of difluprednate as an emulsion, rather than a suspension.”
- Steroid-induced hypertension seen in 8% of the normal population, and is more common in patients with glaucoma.
- Steroid-induced hypertension is “generally not seen until 3 to 6 weeks of corticosteroid use.”
- “Difluprednate was shown to provide better results compared with prednisolone acetate...”
- “We believe the effects seen are the result of the greater anti-inflammatory potency of difluprednate.”

AJO, October, 2011

Loteprednol Etabonate

- Only ester-based, site-specific steroid
- Works at target tissues, and then is quickly metabolized into inert compounds
- LE has high intrinsic activity when applied locally
- 0.5% loteprednol similar in therapeutic equivalence to 1% prednisolone acetate, yet causes little, if any, increase in IOP
- Available as 0.2% (Alrex) ophthalmic suspension, 0.5% Lotemax ointment and 0.5% Lotemax Gel

Lotemax Gel

- A new and improved gel drop formulation of ester-based loteprednol corticosteroid
- This eye drop possesses “adaptive viscosity”
- Provides clear vision in a gel drop delivery system
- No shaking required!
- pH of 6.0-6.5 vs 5.3-5.6 in the suspension
- 70% less BAK than Lotemax suspension
- No increased IOP vs vehicle in phase III study
- FDA approval: post-operative pain and inflammation
- Marketed by B&L as Lotemax Gel in a 5 gm bottle

Loteprednol Ophthalmic Ointment

- The only ester-based steroid ointment available
- It is a 0.5% concentration and preservative-free
- FDA-approved: Post-operative inflammation and pain
- Numerous “off-label” clinical uses: dry eye, allergy, corneal transplant protection, blepharitis, GPC, chronic uveitis, stromal immune herpetic keratitis, Thygeson’s SPK, RCE, augmentation of steroid eyedrop therapy in acute, advanced uveitis or episcleritis, following Betadine EKC Tx, contact dermatitis, and other inflammatory conditions as indicated
- Available in a 3.5 gm ophthalmic tube as Lotemax 0.5% ophthalmic ointment by B&L

Fluorometholone Alcohol

- A progesterone-based steroid
- Useful in treating mild to moderate ocular conditions
- Has a reduced potential to increase IOP
- Available as FML 0.1% suspension and ointment (Allergan) and generic suspensions
- Also available as FML-Forte, a 0.25% suspension (no increase in efficacy beyond the 0.1%. concentration)

Long-Term FML Use After PKP

“In summary, we found that the prolonged use of 0.1% fluorometholone was beneficial for the prevention of rejection after PKP. Because no adverse consequences associated with the use of the eye drops were noted, we recommend continuing the use of low-dose corticosteroids, even in non-high-risk cases.”

Reference: Oph, April 2012

M & T: If such prolonged use of a ketone-based steroid is safe and effective, it would stand to reason that long-term use of loteprednol would be even safer. This has clear implications for long-term use in dry eye-related ocular surface inflammation.

Children and Steroids

- “A tapering regimen of FML for ocular surface disease in children constitutes a safe anti-inflammatory treatment option to avoid steroid-induced glaucoma.”
- “These patients may need prolonged treatment with FML to control the inflammation, a tapering regimen may help avoid steroid-induced glaucoma.”
- No study had an increased IOP above 19mmHg.
  (Reference: BJO; 2011, 95 (11), Pp 1531-1533)

M&T Commentary: We would be much more comfortable using an ester-based corticosteroid such as loteprednol with these patients.

Systemic Prednisone

- Most common Rx’d systemic corticosteroid
- Common initial dosage 40-60 mg
- Available generically in both tablets and DosePaks (5 or 10 mg at 6 or 12 day course)
- Questions to ask before prescribing?
  - Diabetic?
  - Peptic Ulcer Disease?
  - Tuberculosis?
  - Pregnant?

From the “Uveitis Steroid Treatment Trial”

- “The finding that really surprises most clinicians is how little problem we encountered with systemic corticosteroids.”
- “We found that the risk of side effects from systemic steroid therapy is very small, if it is done properly.”

EyeNet, January 2012
Non-ophthalmic steroid: ointment/cream/lotion

- Triamcinolone - moderate potency steroid
- Available in cream, ointment and lotion (0.5%, 0.1%, 0.025%)
- Our favorite: the 0.1% cream

Reference: Drug Facts and Comparisons

Dry Eye Diagnosis: “Symptoms”

“Dry eye disease remains a largely symptomatic diagnosis, without a single diagnostic test.”

Reference: AJO, March 2015. P 470

Lipid-Based Artificial Tears (For Evaporative Dry Eye)

- Vast majority of dry eye patients have MGD
- Meta-stable emulsions are optimum Tx
- Rapidly provides a protective lipid barrier
- Reduces harmful evaporation to prevent tear loss
- Replenishes the complete tear film
  - Systane Balance emulsion (10 ml) – Alcon
  - Refresh Optive Advanced (10 ml) – Allergan
  - Soothe XP (15 ml) – B + L
  - Retaine MGD - OcuSOFT

Aqueous-Based Artificial Tears (For Aqueous Deficient Eye)

- Relatively uncommon cause of dry eyes
- Aqueous-based solutions are 2nd choice
- Rapidly provides ocular surface hydration
- Main ingredients commonly include
  - Cellulose
  - Glycerin
  - Polyethylene Glycol
  - Propylene Glycol
  - Soothe Xtra Hydration (15 ml) – B+L
  - Systane Ultra (15 ml) – Alcon
  - Optive (15 ml) - Allergan
  - Blink (15 ml) – AMO
  - FreshKote (15 ml) – Focus Labs

The Science of Inflammation Suppression

“Given the importance of inflammation in dry eye pathogenesis, various anti-inflammatory agents were used to treat this syndrome. In particular, there is a type-1 level of evidence on corticosteroids efficacy. Among these, 0.5% loteprednol etabonate was effective in reducing signs and symptoms of dry eye.”

Reference: Ophthalmology, January 2015

Our Dry Eye Therapy Algorithm

- All therapy - dry eye included - should be individualized to the patient. That said, here is our usual approach to dry eye management.

  Two Weeks
  - Lipid-Based Artificial Tear
    - Four to six times a day as needed
  
  Four Weeks
  - Lipid-Based Artificial Tear
    - Three to four times a day as needed
  
  Indefinitely
  - Lipid-Based Artificial Tear
    - Two to four times a day as needed
  
  Discontinue Lipidene Gel 0.5% if symptoms improve or patient prefers
  
  Alternately, instill Lotemax Ointment daily at bedtime for three weeks, then M-W-F for three weeks

The risk of increased IOP with Loteprednol is uncommon at high dosage and rare at low dosage. Our experience has been that if an increase in IOP is going to occur, it will do so during the initial four to six week period, and not later.

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Omega-3 essential fatty acids (derived from fish and/or flaxseed oil) can be initiated at any stage, based on clinical judgment.

Two Weeks
- Four Weeks
- Indefinitely

The use of essential fatty acids (derived from fish and/or flaxseed oil) can be initiated at any stage, based on clinical judgment.

*Alternately, instill Lotemax Ointment daily at bedtime for three weeks, then M-W-F for three weeks
Lifitegrast Ophthalmic Solution 5.0% for Treatment of Dry Eye Disease
• Pending FDA approval October 2015
• New and unique mechanism of action addresses the inflammatory pathway early on
• Approval would be for sign and symptomatic relief
• B.I.D. in a preservative-free unit dose container
• To be marketed by Shire Ophthalmics.

Dry Eye Milestones
• “So why does clinical dry eye disease still seem so hard to treat?”
• Reference: Advanced Ocular Care, May/June 2013
• Melton and Thomas answer:
• Because clinicians have failed to embrace the “pulse-dosing” of loteprednol!

Loteprednol Effects on Dry Eye Disease
• “Eyelid scrubs with warm compresses alone are sufficient to modulate the inflammatory process in moderate to severe MGD.”
• Systemic doxycycline has been effective in treating moderate to severe MGD
• Compared with eyelid scrubs with warm compresses alone, additional application of topical 0.5% loteprednol significantly decreased inflammation. There was noticeably improved BUT, corneal and conjunctival fluorescein staining, lid margin abnormality, meibum quality, expressibility, ocular irritation symptoms, and MGD stage.

AJO, December 2014

Loteprednol Effects on Dry Eye Disease
• Using 0.5% loteprednol qid for one month was sufficient to control ocular surface inflammation
• “No cases showing a significant increase of IOP were detected.”
• “Pflugfelder and associates reported no clinically significant changes in IOP in any patient who received topical loteprednol 4 times daily for 1 month.”
• Summary: Loteprednol can provide greater anti-inflammatory effects and clinical benefits through reduction of ocular surface inflammation without serious adverse events.

AJO, December 2014

Alternative Supplementation
• Orally administered omega-3 essential fatty acids
• May take 4-6 months to obtain a significant clinical effect
• Liquid formulations are available for those patients who have difficulty swallowing large capsules.

Benefits of Punctal Plugs
• “Plug placement resulted in greater than 50% improvement of symptoms, improvement in ocular-surface health, reduction in artificial tear use, and improved contact lens comfort in patients with dry eye.”
• “The plugs are well tolerated, with only approximately 10% requiring removal for irritation.”

Ophthalmology, August 2015
Cyclosporine 0.05% Ophthalmic Emulsion

- Topical immunomodulator with anti-inflammatory effects – exact mechanisms unknown
- Indication: “to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation”
- Available in 0.4 ml unit dose vials by Allergan. Supplied in 30-vial tray.
- Dosage: one drop to affected eye(s) b.i.d. Usually takes 4-6 months to reach full therapeutic effect
- Concurrent treatment with ester-based steroid for the first 1-2 months may hasten results

Lacrisert

- A sterile, translucent, rod-shaped, water-soluble, ophthalmic insert (1.27 mm x 3.5 mm) made of hydroxypropyl cellulose 5 mg
- For moderate to severe dry eye sufferers
- Insert into inferior cul-de-sac of eye beneath base of tarsus
- Supplied by Valeant Pharm. in packages containing 60 unit doses, two reusable applicators and a plastic storage container for applicators after use.

Brimonidine Dermatologic Gel

- Used to address the erythema and flushing commonly expressed in facial and eyelid rosacea
- Causes microvascular vasoconstriction
- Comes in a 30 gram tube – applied once daily
- Provides a “somewhat effective” clinical response
- Available as a .33% gel by Gladerma

Reference: The Medical Letter, October 2013

Acute and Chronic Conjunctivitis Due to Over-the-Counter Ophthalmic Decongestants

“Conclusion: Nonprescription decongestant eyedrops can produce acute and chronic forms of conjunctivitis by pharmacological, toxic, and allergic mechanisms. Once recognized, conjunctival inflammation often takes several weeks to resolve.”


Eye Whitener – Luminesse

- Dilute alpha-2 receptor agonist
  - Causes rapid and sustained “whitening” of the bulbar conjunctival microvasculature
- 0.025% brimonidine is the effective dilution
- Does not cause rebound hyperemia like tetrahydrozoline
- Prior to commercialization of Luminesse, “in-office” dilution can be done
- Use a 3 ml sample bottle of aqueous artificial tear, and using a sterile syringe, place 1 ml of 0.1% Alphagan-P into the artificial tear bottle to achieve a 0.025% solution
- Use once daily, usually in the morning, to achieve protracted eye whitening.

Non-Steroidal Anti-Inflammatory Drugs

- Inhibition of prostaglandin synthesis is the mechanism of action.
- They specifically inhibit the action of cyclo-oxygenase, an enzyme vital to prostaglandin synthesis.
- Prostaglandins are powerful mediators of inflammation.
  - Acular (Ketorolac 0.5%) by Allergan and generic
  - Acular LS (Ketorolac 0.4%) - Allergan
  - Acuvail (Ketorolac PF 0.45%)-Allergan
  - Ocuven (Flurbiprofen 0.03%) by Allergan and generic
  - Profenel (Suprofen 1%) by Alcon and generic
  - Voltaren (Diclofenac 0.1%) by Novartis and generic
  - Bromday (Bromfenac 0.09%) by B+L
  - Nevanac (Nepafenac 0.1%) by Alcon
### Nepafenac Ophthalmic Suspensions

- **Nevanac 0.1% AND Ilevro 0.3%**
- **Indication:** Treatment of pain and inflammation associated with cataract surgery
- **Nevanac:** dosed tid; **Ilevro:** once daily
- **Ilevro** is to be prescribed the day before surgery, the day of surgery and then 14 more days
- **BAK 0.005%, pH 6.8, pregnancy category C, pediatric use down to age 10**
- **Marketed by Alcon as Ilevro 0.3% ophthalmic suspension 1.7 ml and 3 ml**

### Bromfenac Ophthalmic Solutions

- **Bromday 0.09% and Prolensa 0.07% (22% less concentration)**
- **Indication:** Treatment of pain and inflammation associated with cataract surgery
- **Both:** dosed once daily
- **Both** are prescribed the day before surgery, the day of surgery and then 14 more days
- **BAK 0.005% BAK pH 7.8, pregnancy category C, pediatric use down to age 18**
- **Marketed by B&L at Prolensa 0.07% ophthalmic solution (3ml)**

### BromSite (bromfenac ophthalmic solution) 0.075%

- **Bromfenac 0.075% in the DuraSite vehicle.**
- **Indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.**
- **The first “drug-use-in-pregnancy rule” indication**
- **Dosing:** One drop of BromSite applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days postsurgery.
- **Supplied as 5 mL in a 7.5 mL bottle by Sun Pharma**