Ocular Surface Disease
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Dry Eye Syndrome: An Ocular Surface Inflammatory Disease (OSID)

- Dry Eye Syndrome is a common and under-recognized ocular surface inflammatory disease (OSID)
- Inflammation is a hallmark of dry eye
- A group of disorders of the tear film due to reduced tear production or excessive tear evaporation
- Affects tear quantity and quality
- Associated with symptoms of ocular discomfort
- Associated with significant ocular morbidity


Epidemiology of Dry Eye Syndrome

- Approximately 25% of eye care visits are due to Dry Eye
- Up to 40 million Americans may either have symptoms of Dry Eye or are at risk for it
  - Incidence of Dry Eye increases with age
    - Up to 51% of patients older than 65 years
    - Up to 31% of women between 40 and 59 years of age
  - Despite these numbers, Dry Eye remains remarkably under-diagnosed


Dry Eye Syndrome: Under-recognition Due to Self-Treatment

- Many patients use OTC artificial tears and lubricants, which are mostly palliative
  - Estimated artificial tears USA sales >$145.4 million in 2005
- Self-treatment with OTC agents may delay diagnosis and effective therapy
- Untreated inflammation associated with Dry Eye can lead to significant irreversible ocular damage

2. IMS Dataview 2005. OTC = over-the-counter.

Dry Eye Syndrome: Predisposing Factors

- Age
- Gender
- Environment
- Anterior segment disease
- Medications
- Contact lenses
- Surgery
- Systemic diseases

Systemic Diseases Associated With Dry Eye Syndrome

- Diabetes mellitus
- Acne rosacea
- Thyroid disease
- Lymphoma
- Inflammatory diseases
  - Allergy
  - Asthma
  - Vasculitis
- Sjögren’s syndrome
- Autoimmune diseases
  - Rheumatoid arthritis
  - Lupus
- Neuromuscular disorders
  - Parkinson's disease
  - Bell's palsy

Ocular Diseases Associated With Dry Eye Syndrome

- Dry Eye can exist in association with several other ocular surface inflammatory diseases (OSIDs)
  - Seasonal allergic conjunctivitis (SAC)\(^1\)
  - Giant papillary conjunctivitis (GPC)\(^1\)
  - Blepharitis\(^2,3\)
  - Meibomitis\(^2,3\)


Adapted with permission from Lemp MA. *CLAO J*. 1995;21:221-231.

Dry Eye Syndrome: Classification

Inflammation Underlies Dry Eye Syndrome

- Inflammation affects the external ocular surface components\(^1\)
  - Eyelids
  - Bulbar and palpebral conjunctival epithelium
  - Lacrimal and meibomian glands
  - Corneal epithelium
- Inflammation affects tear production\(^1,2\)
  - Decreased quantity of "normal" tears
  - Excessive "dysfunctional" tears/mucus

Neural Regulation of Normal Tear Production

Inflammation as an Underlying Factor in the Pathophysiology of Dry Eye Syndrome\(^1,3\)

- Inflammatory Cellular Infiltration
- Tissue Scarring
- Lacrimal Gland Dysfunction
- Meibomian Gland Dysfunction
- Decreased Aqueous Tear Production
- Defective Tear Lipid Film/Layer
- Increased Evaporative Loss
Dry Eye Syndrome: Tear Film Inflammatory Response

- Tear film has a complex biochemical structure\(^1\)
  - External layer that covers and protects the ocular surface epithelium
- Abnormality in tear film composition leads to inflammation\(^2\)
- Increased concentration of inflammatory cells and other mediators in tears—“hot” tears\(^2\)
- Inflammation of the tear film can affect the tear-secreting glands
- Abnormal tear film composition, production, and clearance perpetuates the inflammatory cycle → chronic inflammation\(^3\)

Inflammatory Mediators of the Tear Film\(^1-4\)

- T-cells
- Matrix-degrading enzymes
  - \(\uparrow\) MMP-9
  - \(\uparrow\) Protease activity
- Inflammatory cytokines
  - \(\uparrow\) IL-1β
  - \(\uparrow\) TNF-α
  - \(\uparrow\) TGF-β
  - \(\downarrow\) IL-1RA
- Adhesion molecules
  - ICAM-1
  - VCAM-1
- Immunoglobulins
  - \(\uparrow\) IgM
  - \(\uparrow\) IgG
  - \(\downarrow\) IgA
- Proinflammatory neural transmitters
  - Substance P
  - CGRP

Inflammatory Cycle of Dry Eye Syndrome

Misdiagnosis of Dry Eye Syndrome

- Diagnosis is primarily based on clinical signs and symptoms reported by patients\(^1,2\)
- Poor correlation exists between clinical signs and reported symptoms\(^1\)
- Several tests are available, but not one specific diagnostic test\(^1-3\)
- Misdiagnosis leads to under-recognition and under-treatment
- Long-standing, untreated inflammation → ocular complications

Inflammation Associated with Dry Eye Syndrome Can Lead to Ocular Complications\(^1,2\)

- Infection
- Ocular surface keratinization
- Corneal ulceration
- Conjunctival squamous metaplasia

These conditions can result in permanent structural damage with possible loss of visual function\(^7\)
Need for Early Diagnosis and Treatment

- Inflammation is often present long before clinical signs
- Goal is to arrest inflammation before damage is irreversible
  - Institute immediate therapy that is safe and effective
  - Ensure adequate dose and duration of therapy
- Early diagnosis and proper treatment lead to better outcomes

Dry Eye Syndrome: Optimal Diagnostic Approach

- Complete patient history and physical examination
- One or more diagnostic tests
  - Completed over a period of time
  - Best approach to increase sensitivity and specificity in diagnosis

Diagnostic Tests for Dry Eye Syndrome

- Standard in-office diagnostic tests
  - Schirmer test
  - Fluorescein tear breakup time
  - Ocular surface dye staining
    - Rose bengal
    - Lissamine green
    - Fluorescein
- Other available (out-of-office) diagnostic tests
  - Tear film osmolarity
  - Tear lactoferrin
  - Impression/brush cytology

Dry Eye International Task Force: Diagnostic Recommendations

- A panel of experts achieved consensus on diagnostic parameters for Dry Eye
- Dry Eye Syndrome severity classification, based on signs and symptoms

| Level 1 | Mild to moderate symptoms
| Level 2 | Moderate to severe symptoms
| Level 3 | Severe symptoms
| Level 4 | Extremely severe symptoms/altered lifestyle

Dry Eye International Task Force: Therapeutic Recommendations

- A panel of experts achieved consensus on therapeutic parameters for Dry Eye
- Treatment options corresponding to the 4 severity levels

| Level 1 | Preserved tears
| Level 2 | Unpreserved tears
| Level 3 | Unpreserved tears
| Level 4 | Systemic antiinflammatory therapy

Dry Eye Syndrome: Diagnostic Recommendations

- Standard in-office diagnostic tests
- Other available (out-of-office) diagnostic tests

Dry Eye Syndrome: Therapeutic Recommendations

- Treatment options corresponding to the 4 severity levels
- Preserved tears
- Unpreserved tears
- Unpreserved tears
- Systemic antiinflammatory therapy
Dry Eye Syndrome: Current Treatment Options1-3

- Medical management
  - OTC agents
  - Prescription agents
  - Occlusive spectacles/goggles
  - Moisture chambers
- Surgical management
  - Lid abnormality correction
  - Punctal occlusion for severe cases
  - Tarsorrhaphy for severe cases

Dry Eye Syndrome: Pharmacologic Therapy1-3

- Topical corticosteroids
- Immunomodulation therapy
- Secretagogues
- Mucolytics
- Cholinergic agonists
- Antibiotics
- Systemic anti-inflammatory therapy

Immunomodulation Therapy

- Cyclosporine ophthalmic emulsion 0.05%
  - Approved by the FDA in December 2002 for treatment of Dry Eye1
  - Immunosuppressive (T-cell specific) agent1
    - Inhibits T-cell activation 2-4
    - Downregulates T-cell–mediated cytokines 2-4

Cyclosporine: Pivotal Studies1

- Cyclosporine ophthalmic emulsion 0.05% was compared with placebo for the treatment of moderate to severe keratoconjunctivitis sicca
- Four randomized, adequate, well-controlled, multicenter studies (n=1200)
- Patients treated with immunomodulator or vehicle twice per day for 6 months
- At 6 months, 15% of treated versus 5% of placebo patients had an increase in Schirmer wetting test of 10 mm
- The most common adverse event was ocular burning in 17% of patients treated with cyclosporine

Topical Corticosteroids

- Broad-spectrum, anti-inflammatory ophthalmic products1
- Mechanism of action spans virtually every aspect of the inflammatory response1
  - Nuclear
    - Decreases production of inflammatory precursor proteins
  - Cellular
    - Suppresses proliferation of mast cells and lymphocytes1
    - Biochemical
      - Inhibits synthesis and enhances breakdown of histamine1
    - Immediately effective2

Percentage of Patients With a Positive Schirmer Wetting Test (10 mm)
Topical Steroids Work Early to Block Multiple Pathways of Inflammatory Cascade

Membrane Phospholipids

- Phospholipase A2
- Arachidonic Acid
- Lipoxygenase
- Hydroperoxides
- Leukotrienes
  - LTC4, LTD4, LTE4, LTE5
- Prostaglandins
  - PGF2, PGD2, PGE2
- Cyclooxygenase
- Cyclic Endoperoxides
- Prostacyclin
  - PCI2
- Thromboxane A2
  - TXA2
- Histamine
-mast cells
- Membrane Stabilization
- T-Cells
- Membrane Phospholipids
- Tyrosine Kinase
- Progenitor Cell Proliferation
- Mast Cell
- Membrane Phospholipids

Topical Corticosteroids Work Early to Block Multiple Pathways of Inflammatory Cascade

Topical Corticosteroids: Limitations

- With most topical corticosteroids, complications are a concern with long-term use
  - Increased IOP
  - Cataract formation
  - Exacerbation of viral and/or fungal infections

Need for an optimal corticosteroid that allows for safe long-term use

The Ideal Ophthalmic Corticosteroid Therapy for Dry Eye Syndrome

- Broad-spectrum anti-inflammatory properties
- Rapid onset of action
- Targeted, site-specific activity
- Complete symptom control
  - eg, burning, stinging
- Potent, but safe for prolonged use
- Minimal adverse events
- Works synergistically with immunomodulators

The Role of LOTEMAX® in Dry Eye Inflammation

Loteprednol Etabonate: The Only Ester Corticosteroid

- Unique topical steroid
  - Retrometabolic drug design
  - Modification of an existing molecule to reduce or eliminate unwanted adverse events
  - Prednisolone derivative
  - Position 20 ester group replaces the ketone group

Loteprednol Etabonate: Clinical Benefits of the Only Ester Corticosteroid

- Benefits of the ester group
  - Efficacy
    - High lipophilicity leads to better penetration
    - Lipophilic index 10 times higher than dexamethasone
    - Rapid targeted receptor binding leads to enhanced therapeutic effect
    - 4.3 times greater binding affinity to steroid receptors than dexamethasone
  - Safety
    - Unlike any other corticosteroid, loteprednol etabonate only becomes activated when bound to receptor
    - Rapid inactivation of unbound drug by circulating esterases leads to an inactive metabolite and minimal adverse events
    - Significantly reduced incidence of IOP increase
    - Decreased risk of cataract
Lotemax® for the Treatment of Dry Eye Inflammation

• Lotemax was compared with placebo for the treatment of the inflammatory component of Dry Eye in patients with delayed tear clearance
• Randomized, double-masked, placebo-controlled, multicenter comparison
• Patients with Dry Eye (n=66)
  – 32 patients treated with Lotemax
  – 34 patients treated with placebo
• Subjects received either Lotemax or placebo QID in both eyes for 4 weeks

Efficacy of Lotemax® in Patients With Moderate Symptoms of Dry Eye Inflammation

Subjects With Corneal Staining Score ≥10 and Conjunctival Hyperemia Score ≥2 at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Primary Subjective Outcome 1</th>
<th>Primary Objective Outcome 1</th>
<th>Central Corneal Staining</th>
<th>Inferior Tarsal</th>
<th>Inferior Bulbar</th>
<th>Nasal Bulbar</th>
<th>Redness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lotemax</td>
<td>-11.1</td>
<td>-35.7</td>
<td>-21.1</td>
<td>-25.0</td>
<td>-28.6</td>
<td>-47.1</td>
<td>4.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>-50.1</td>
<td>-22.2</td>
<td>-10.1</td>
<td>-3.8</td>
<td>0.0</td>
<td>4.4</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Primary Objective Outcome 1: Improvement from Baseline

Efficacy of Lotemax® in Patients With Moderate Symptoms of Dry Eye Inflammation (cont)

• The Lotemax-treated group showed greater improvement than the vehicle group in both primary subjective and primary objective outcomes
• Lotemax resulted in greater improvement than the vehicle group in multiple indices of conjunctival hyperemia
• Lotemax showed much greater improvement than the vehicle group in central corneal staining score
• Improvements achieved in the Lotemax-treated group at 2 weeks were maintained after 4 weeks of treatment when compared with the vehicle group

Safety of Lotemax® in Patients With Moderate Symptoms of Dry Eye Inflammation

• Reported adverse events were similar for both the Lotemax and the placebo groups
• There were no clinically significant IOP changes in either group
• There were no signs of cataract formation
• Safety of loteprednol etabonate has been further supported by several long-term follow-up studies

Efficacy and Safety of Lotemax® in Patients With Moderate Symptoms of Dry Eye Inflammation

• When used as monotherapy, Lotemax resulted in greater improvement in objective signs and symptoms of Dry Eye than placebo at both 2 and 4 weeks
• Lotemax also improved the surface regularity index and corneal staining, which are correlated with visual acuity
• Lotemax demonstrated no clinically significant IOP elevation following 1 month of therapy for Dry Eye
• Treatment of Dry Eye patients with Lotemax beyond 2 weeks carries an excellent benefit-to-risk ratio

4. IOP = intraocular pressure.
Lotemax®: Potential Use of Concomitant Therapy in Dry Eye Inflammation

- Topical corticosteroids have a rapid onset of action for faster relief and can be used concomitantly with cyclosporine.
  - Cyclosporine may require up to 6 months to produce a clinically therapeutic effect.
- In clinical practice, concomitant therapy of Lotemax and cyclosporine for Dry Eye has been reported to be far more effective than either therapy used alone.
  - Clinical trials have yet to be completed.
- Lotemax may help minimize adverse events such as burning and stinging associated with cyclosporine.
- Lotemax may help improve patient compliance and satisfaction with topical cyclosporine therapy.
- Lotemax is the #1 corticosteroid used in combination with cyclosporine for the treatment of Dry Eye Inflammation.

Zylet®: Site-Active Corticosteroid Plus Broad-Spectrum Aminoglycoside

- Loteprednol Etabonate 0.5%:
  - Site-active corticosteroid
  - Inhibits inflammatory response to a variety of inciting agents
    - May act by inducing phospholipase A2 inhibitory proteins, collectively known as lipocortins.
- Tobramycin 0.3%:
  - Broad-spectrum aminoglycoside
  - Inhibits bacterial protein synthesis
    - Binds to bacterial ribosomes.

Loteprednol Etabonate 0.5%:
First and Only Ester Corticosteroid

Ester vs. Ketone Corticosteroids

- Ester
  - Prednisolone
  - Fluorometholone
  - Dexamethasone
  - Medrysone
  - Rimexolone

- Ketone
  - Loteprednol

Common Tobramycin Susceptible Bacterial Pathogens

- Staphylococci
- Streptococci
- Pseudomonas aeruginosa
- Escherichia coli
- Klebsiella pneumoniae
- Enterobacter aerogenes
- Proteus mirabilis
- Morganella morganii
- Proteus vulgaris (most strains)
- Haemophilus influenzae
- Haemophilus aegyptius
- Moraxella lacunata
- Acinetobacter calcoaceticus
- Neisseria (some species)

Key Zylet Clinical Studies:
Efficacy and Safety

- Tobramycin: No impact on Loteprednol Etabonate 0.5% Bioavailability
- Analysis of intent-to-treat population.

Loteprednol Etabonate: No Impact on Tobramycin Antimicrobial Activity

- Zylet was tested versus tobramycin ophthalmic solution, USP, 0.3%1
- 20 Test organisms were evaluated in vitro1
- Zylet was found to have equivalent antimicrobial activity as tobramycin alone1

Clinical Studies

Efficacy

How Effective is Loteprednol Etabonate 0.5% in Treating Anterior Chamber Inflammation Following Cataract Surgery?

Two Studies:
Novack GD1; Stewart R2

Objective:
Two identical, randomized, placebo-controlled, double-masked, parallel-group, multicenter trials were carried out to determine the efficacy of loteprednol etabonate 0.5% in reducing anterior chamber inflammation following cataract surgery with intraocular lens implantation1,2

Loteprednol Etabonate 0.5%: Post-cataract Surgery Inflammation

Resolution of anterior chamber inflammation1

<table>
<thead>
<tr>
<th>Visit</th>
<th>Treatment Group</th>
<th>Patients at Risk (combined), N</th>
<th>Resolution of inflammation, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Loteprednol etabonate 0.5%</td>
<td>211</td>
<td>30 (14)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>213</td>
<td>13 (6)</td>
</tr>
<tr>
<td>3</td>
<td>Loteprednol etabonate 0.5%</td>
<td>198</td>
<td>77 (39)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>175</td>
<td>31 (16)</td>
</tr>
<tr>
<td>4</td>
<td>Loteprednol etabonate 0.5%</td>
<td>191</td>
<td>123 (64)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>146</td>
<td>57 (39)</td>
</tr>
</tbody>
</table>

Final visit:
Loteprednol etabonate 0.5%: 211, 128 (60)*
Placebo: 213, 81 (39)

Was Loteprednol Etabonate 0.5% Found to be Safer Than Prednisolone Acetate in Treating Acute Anterior Uveitis?

Two Studies:
Novack GD1

Objective:
Two virtually identical, randomized, active-controlled, double-masked, parallel-group, multicenter trials were carried out sequentially to determine the safety and efficacy of loteprednol etabonate 0.5% in the treatment of acute anterior uveitis1,2

Loteprednol Etabonate 0.5%:
Post-cataract Surgery Inflammation

Lower incidence of treatment failure1

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Patients at Risk (combined), N</th>
<th>% Treatment Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loteprednol etabonate 0.5%</td>
<td>211</td>
<td>20 (%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>213</td>
<td>30 (%)</td>
</tr>
</tbody>
</table>

*Significant difference in favor of loteprednol etabonate 0.5% (P<.001).
Loteprednol Etabonate 0.5%: Acute Anterior Uveitis

Anti-inflammatory efficacy1,2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Loteprednol Etabonate 0.5%</th>
<th>Prednisolone Acetate 1.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell</td>
<td>72% (58/81)</td>
<td>87% (77/89)</td>
</tr>
<tr>
<td>Flare</td>
<td>66% (52/79)</td>
<td>82%* (72/88)</td>
</tr>
<tr>
<td>Pain</td>
<td>90% (69/77)</td>
<td>85% (75/88)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>79% (58/73)</td>
<td>78% (64/82)</td>
</tr>
</tbody>
</table>


Loteprednol Etabonate 0.5%: Acute Anterior Uveitis

Resolution of anterior chamber cell reaction1

Intent-to-treat N=170

*P=0.015

†36 to 72 hours after end of treatment


Loteprednol Etabonate 0.5%: Acute Anterior Uveitis

Resolution of anterior chamber flare reaction1

Intent-to-treat N=170

*P=0.017

†36 to 72 hours after end of treatment


Two Studies:
Asbell P1; Friedlaender MH2

Objective:
Two randomized, double-masked, placebo-controlled, parallel-group, prospective, multicenter trials with identical designs were carried out to determine the efficacy of loteprednol etabonate 0.5% in the treatment of contact lens-associated giant papillary conjunctivitis1,2

How Effective is Loteprednol Etabonate 0.5% in the Treatment of Contact Lens-associated Giant Papillary Conjunctivitis?

Loteprednol Etabonate 0.5%: Giant Papillary Conjunctivitis

Significant improvement in primary efficacy parameters1-3

<table>
<thead>
<tr>
<th>Response</th>
<th>Number of Patients</th>
<th>Papillae</th>
<th>Itching</th>
<th>Lens Intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loteprednol etabonate 0.5%</td>
<td>221</td>
<td>76%</td>
<td>94%</td>
<td>91%</td>
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<tr>
<td>Placebo</td>
<td>222</td>
<td>51%</td>
<td>79%</td>
<td>78%</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>


Loteprednol Etabonate 0.5%: Giant Papillary Conjunctivitis

Significant improvement in secondary efficacy parameters1-3

<table>
<thead>
<tr>
<th>Response</th>
<th>Number of Patients</th>
<th>Investigator Global Assessment</th>
<th>Palpebral Injection</th>
<th>Bulbar Injection</th>
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<tbody>
<tr>
<td>Loteprednol etabonate 0.5%</td>
<td>221</td>
<td>85%</td>
<td>68%</td>
<td>79%</td>
</tr>
<tr>
<td>Placebo</td>
<td>222</td>
<td>58%</td>
<td>48%</td>
<td>43%</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

### How Effective is Loteprednol Etabonate 0.5% in the Treatment of Contact Lens-Associated Giant Papillary Conjunctivitis?

**Key results:**
- Patients on loteprednol etabonate 0.5% experienced significantly greater improvement in all 3 primary efficacy variables (papillae, itching, lens intolerance) compared with those on placebo.
  - Intergroup differences favored loteprednol etabonate 0.5% by 25% for reduction in size and severity of papillae, 15% for reduction in itching, and 13% for improved contact lens tolerance ($P < .001$ for each).
  - Two additional studies found that loteprednol etabonate 0.5% was both well tolerated and clinically effective in the treatment of giant papillary conjunctivitis.

### How Effective is Loteprednol Etabonate 0.5%—the Anti-inflammatory Component of Zylet—in Preventing Seasonal Allergic Conjunctivitis?

**One Study:**

**Objective:**
A randomized, double-masked, placebo-controlled, parallel-group, multicenter trial was carried out to determine the efficacy of loteprednol etabonate 0.5% as prophylaxis against seasonal allergic conjunctivitis.

**Key result:**
- Patients in the loteprednol etabonate 0.5% group never developed moderate or severe ocular signs and symptoms of allergy during the peak pollen season vs. patients in the placebo group.
  - Loteprednol etabonate 0.5% was effective in the prophylaxis of seasonal allergic conjunctivitis.

### Loteprednol Etabonate 0.5%: Seasonal Allergic Conjunctivitis

**Significant improvement in primary efficacy variables**

![Graph showing significant improvement in primary efficacy variables](image)

### Clinical Studies

**Adverse Events**

- Only 0.2% of patients exhibited a serious adverse event considered possibly or probably related to study medication.
- All of these patients experienced complete resolution upon discontinuation of treatment.

### Loteprednol Etabonate 0.5%: Low Incidence of Adverse Events

- Adverse events occurring in 5% to 15% of patients:
  - Abnormal vision/blurring
  - Epiphora
  - Burring on instillation
  - Foreign body sensation
  - Itching
  - Injection
  - Dry eyes
  - Photophobia
- Only 0.2% of patients exhibited a serious adverse event considered possibly or probably related to study medication.
- All of these patients experienced complete resolution upon discontinuation of treatment.
Two Studies:
Bartlett JD\(^1\); Novack GD\(^2\)

**Objective:**
Both were randomized, double-masked, crossover studies of populations of known steroid responders and an analysis of controlled, randomized trials in subjects treated for ≥28 days were carried out to determine the safety of loteprednol etabonate 0.5% vs. prednisolone acetate 1.0% with regard to elevation in intraocular pressure\(^1,2\)

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### What Impact Does Loteprednol Etabonate 0.5% Have on Intraocular Pressure?

#### Loteprednol Etabonate 0.5%:

**Intraocular Pressure**

- **Low incidence of elevation with long-term treatment**\(^1\)

#### Key results:
- The mean intraocular pressure elevations induced in known steroid responders were neither statistically nor clinically significant after 6 weeks with loteprednol etabonate 0.5%
- Significant elevations in prednisolone acetate group (18.1 mm Hg at baseline vs. 27.1 mm Hg on day 42 \(P<.05\))\(^1\)
- An analysis of controlled, randomized trials demonstrated a significant elevation in intraocular pressure in only 1.7% of patients on loteprednol etabonate 0.5% compared with 6.7% of patients on prednisolone acetate 1.0% \(^2\)

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### Clinical Safety

- Studied in >2000 patients in 20 clinical studies\(^1,3\)
- Ocular Adverse Events:
  - Very low incidence of IOP rise that was generally transient in nature\(^1,2\)
  - Only 15 (1.7%) of 901 patients treated 28 days or longer had an IOP rise >10 mm Hg\(^1\)
  - 11 of 15 patients with a clinically significant (>10 mm Hg) IOP response were in GPC studies\(^1\)
- Patients were allowed to wear lenses indicating possible reservoir effect of lenses

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### Tobramycin 0.3%:

**Low Incidence of Adverse Events**

- Adverse events occurring in <3% of patients\(^1,2\):
  - Hypersensitivity reactions
  - Local ocular toxicity
  - Swelling and/or itching of eyelids
  - Conjunctival erythema
Zylet®: Adverse Reactions

42-Day Safety Study

<table>
<thead>
<tr>
<th>Ocular Events</th>
<th>Zylet n=112</th>
<th>Placebo n=56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection</td>
<td>21%</td>
<td>29%</td>
</tr>
<tr>
<td>≥ IOP</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Average IOP Increase</td>
<td>(1.6 mm Hg)</td>
<td>(1.1 mm Hg)</td>
</tr>
<tr>
<td>SPK</td>
<td>13%</td>
<td>18%</td>
</tr>
<tr>
<td>Sting/Burn</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>All Other</td>
<td>&lt;4%</td>
<td>---</td>
</tr>
</tbody>
</table>

Patients at Risk for Elevated IOP Associated with Steroid Use

- 14 to 22 million people who are steroid responders
- 3 to 6 million people with ocular hypertension
- 3 million people with glaucoma

Proven Clinical Experience with Tobramycin

- Broad-spectrum aminoglycoside antibiotic with over 20 years of real world experience
- Active against both Gram-positive and Gram-negative ocular pathogens
- Binds to bacterial ribosomes, inhibiting protein synthesis
- Generally bacteriostatic, but may be bactericidal in high doses
- Corneal penetration enhanced by lipid solubility
- Low serum concentrations with ocular administration

Case Study #1

- 49 y/o myopic female seen in refractive consultation. History of contact lens intolerance over past 5 years with giant papillary conjunctivitis (GPC)
- Medical history: Asthma; recent onset of menopause

- Mild GPC
- Normal tear meniscus
- BCVA 20/25 OU
- 3+ lissamine green conjunctival staining
- 1+ fluorescein corneal staining
- Schirmer with anesthesia 5 OD/4 OS
- Ocular Surface Disease Index (OSDI) = 0.39
  - Corresponds to severe dry eye
  - Scale 0-1, normal subjects score 0.05-0.10

◆ 3+ Conjunctival Staining
• Started on Systane qid
• One month later:
  – 2+ lissamine green conjunctival staining
  – 1+ fluorescein corneal staining
  – Schirmer 5 OD/5 OS
• Patient started on topical lotenpredenol (Lotemax) BID and cyclosporine BID

• Two months later:
  – BCVA 20/20 OU
  – 1+ lissamine green conjunctival staining
  – No fluorescein corneal staining
  – Schirmer 11 OD/10 OS
  – GPC resolves
• Patient undergoes uneventful LASIK
  – Lotemax/cyclosporine treatment made this patient into a LASIK candidate
Case Study #2

- 42 y.o. Caucasian Male
- CC: FB Sensation, Dry burning eyes
- Eyes constantly red
- Can’t go outside - eyes hurt!

Predisposing factors

- Age
- Gender
- Environment
- Anterior Segment Disease
- Medications
- CL Wear
- Refractive surgery
- Systemic Disease

Systemic Disease

- Diabetes
- Arthritis
  - Sjogren’s
- Thyroid Eye Disease

- Most missed systemic caused?
- Rosacea

Rosacea

- Erythema
- Telangiectasia
- Pustules
- Prominent sebaceous glands
- Rhinophyma
Rosacea

- Presentation
- Women: cheeks
- Men: nose

Rosacea

- Meibomian gland dysfunction
- Dry eye
- Blepharitis
Ocular Rosacea

- 58% of all rosacea patients
- Presenting sign in:
- 20%! 
Rosacea: Treatments

- Tetracyclines: Doxycycline 50mg bid x 1-2 months then qd
- Metrocream
- Education
- Periostat long term (20mg doxycycline)

Tetracycline MOA

- Accumulation in Oil Glands
- Anti-inflammatory component
- Regulate enzymatic activity of staph

Cautions

- Photosensitivity
- Chelates with dairy products, antacids etc.
- Minocycline may cause vestibular toxicity
- Number one drop-out reason? - 25%

Which of the following patients could be given Doxycycline

A. Pregnant woman
B. 23 y.o. female with Chlamydia
C. 8 y.o. child
D. 52 y.o. male with acne rosacea

Tetracycline

- Pregnancy ratings:
  - A, B, C, D, X
- Rating on tetracycline: D

Which of the following medications should someone on doxycycline avoid

A. Antidepressants
B. Antacids
C. Tagamet
D. Birth control pills
Which of the following complications may be related to doxycycline?

A. Dry eye  B. Blepharitis  
C. Pseudotumor Cerebri  D. Iritis

Nutritional Supplements: Essential fatty acids

- Flaxseed oil (1000 mg bid if tablet form)
- Castor oil
- Fish oils
- Omega-3 fatty acids - linoleic acid

Recommendation: Combination flax/fish oil (500mg) begin qd then move to bid/tid

Case 3

- So why does her left eye hurt more than OD even though OD looks worse?
- How do you counsel this patient?
  - NPAT
  - Restasis/Steroids
  - BSCL/Moisture goggle
- Do you use for systemic therapy?
  - Hormone work-up
  - Nutritional Support
  - DCN
- What do you do about the filaments?
- Do you plug immediately?

Case #

- 56 YOWF presents with red eye and moderate pain
- VA 20/25 bcc
- History of "burned-out" arthritis
- Slex as shown
Case #

- Differential diagnosis
  - Allergic conjunctivitis
  - Viral conjunctivitis
  - Episcleritis
  - Scleritis
  - Phenylephrine testing
- Treatment and diagnostic management

Lab Workup

- ACE
- ANA
- CBC w diff
- Serum Lysozyme
- RF
- HLA-B27
- ESR
- VDRL/FTA-ABS

Case #

- 36 yowf 30-day extended wear FND 8.4 -6.50 OU normal VA
- Patient reports increased ocular comfort with contact lenses on.
- Microcystic formation anterior cornea
- Stain with nafl
- Differential Dx
  - SIHI immune reaction or other unknown mechanism
  - Thygesson's corneal dystrophy
Case #
- 38yowm
- FND -5.00 OU
- 30 day EW x 2 years
- Presents with red, light sensitive eye
- 2 days duration
- No lens x 24 hours
- Photos, management

Case Study #?
- 42 y.o. male 1 month post LASIK
- Transient Blur – worse in the evening
- Throughout the day
- No burning, stinging, dryness etc.

Case #
- Infectious or inflammatory?
- SiHi modulus
- Treatment-
  - 3d vs 4th generation FQ
  - Steroids and when?