Off-Label Use of Cyclosporine in Eye Care

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The Immune System
- Incredibly powerful
- Exists to detect & destroy invaders
- Prehistoric focus – parasites
- MHC identify “self”-prevent attack
- Genetic disposition to fail in detecting self- “auto-immunity”

Lymphocytes and Immunology
- Part of vertebrate immune system
  - Large granular (natural killer cells)
    - Target cells lacking MHC
      -- Tumor cells & infected cells
  - Small lymphocytes
    - T cells (mature in thymus)
      -- Cell-mediated immunity
    - B cell (mature in bone marrow)
      -- Humoral immunity (antibody formation)

B-Lymphocytes On The Attack!
- Recognize “non-self” antigens
- B lymphocytes ➔ plama cell
  - Produce antibodies (lots)
  - Direct action on cell
  - Attract phagocytes
  - Activate complement system
    - Create hole in cell to release contents

T-Lymphocytes On The Attack!
- Recognize “non-self” antigens on cell surfaces
- T helper cells (CD4)- direct action of other T cells, other immune cells
- T cytotoxic cells ➔ toxic substances- directly kill
  - Viral- infected, tumor, allograft cells

TRACY
- 33 year old female presents w/ irritation OD for three days.
- OS essentially blind secondary to unknown corneal condition
- Hx of atopy, asthma, dermatitis
- VA OD 20/30 OS 20/200
Tracy: Initial Presentation

OD

Tracy: Initial Presentation

OS

Tracy: OD Initial Presentation

Diagnosis- OS old corneal pannus
Diagnosis- OD
- Atopic dermatitis
- Atopic keratoconjunctivitis
- Toxic corneal epitheliopathy

Management
- Lotemax Q 2 hours
- Elestat Q 12 hours
- Non-preserved artificial tears PRN

Tracy

- After initial therapy, corneal changes are stable, but not improved
- Patient complains of reduced vision and discomfort
- VA OD 20/60 OS 20/200
- Plan:
  - Add Restasis Q 12 hrs OU

Tracy

- After 4 days of therapy
  - Lotemax Q 4 hours
  - Elestat Q 12 hours
  - Non-preserved artificial tears
  - Restasis OU Q 12 hours
- VA OD 20/30 OS 20/200
- Comfort much better
- Objective vision better
- Ulcer beginning to re-epithelialize
Tracy’s Eyelids
Pre       Post

Tracy’s Right Cornea
Pre       Post

Tracy’s Shield Ulcer
Pre       Post

Tracy; Two Months Ago

Going Off Label
• Very common in health care
• Prescriber must:
  ➢ Understand the mechanisms of action of the drug
  ➢ Know the disease processes and any immunologic cells involved
  ➢ Know how to differentiate a good from a bad clinical result
  ➢ Advise the patient of “off label use” and document!

Restasis
Cyclosporine A emulsion 0.05%
• Approved for inflammatory dry eye April, 2003
• Cyclic peptide (macrolide) produced by fungi Tolyopcladium Inflatum Gams
• Reversible immunomodulator of T-lymphocytes and B-lymphocytes
• Blocks CD4+ T-lymphocyte proliferation
• Inhibits activation of eosinophils and mast cells
How Does Restasis Work?

Restasis contains the immunomodulator cyclosporine. Cyclosporine modulates inflammation - the underlying cause of dry eye.

T-lymphocytes
- Leukocytes produced in bone marrow that mature in the thymus.
- Activate many other cells including macrophages, eosinophils.
- Important in pathogenesis of AKC, VKC, other ocular inflammatory conditions.
- Involved in formation of infiltrates.

Eosinophils
- Comprise 2-5% of circulating cells.
- Kill cells or organisms too large to be phagocytosed (parasites).
- Release, peroxidase, histaminase, and proteolytic enzymes.
  - Eosinophil major basic protein.
- Present, but not active in Type I allergic response.

Atopic Keratoconjunctivitis (AKC)
- Occurs in 25% to 40% of patients with atopic dermatitis.
  - Hyperplasia of dermis, hyperkeratosis.
  - Sites include antecubital, popliteal flexures and periorcular dermis.
- More prevalent in dry, warm climates.
- Strong genetic predisposition.
- Tends to be bilateral.
- Peak incidence is in persons aged 30-50 years.
- Predominantly mediated by T-lymphocytes.
- Eosinophils responsible for tissue damage.
- Histology suggests type IV hypersensitivity.

Atopic Dermatitis
Twenty-two patients with AKC refractory to topical steroid treated with cyclosporine 0.05% or with placebo. After 4 weeks, cyclosporine treated group had fewer signs, symptoms, and no adverse effects observed.

“This formulation seems valuable in the treatment of topical steroid-resistant AKC. Its efficacy in the long-term treatment of patients with topical steroid-dependent or topical steroid-resistant AKC as a first-line agent should be considered, and warrants an additional, larger study.”

AKC Management
- Patient education - a chronic disease
- Topical steroids
  - Prednisolone phosphate 1% Q 2 hr
  - Lotepredolol Q 2 hr
  - Taper when condition stabilized - cornea
- Restasis 0.05% Q 12 hrs long-term
- May benefit from “mast cell stabilizer” for anti-inflammatory effects
- 27% have some long-term VA loss
- Tacrolimus ointment Q 12 hrs for skin changes topical

Vernal Keratoconjunctivitis (VKC)
- Chronic, bilateral condition
- Related to atopy
- Primary signs & symptoms
  - Itching
  - Injection
  - Giant papillae on upper tarsus
  - Excess mucous production
- Occurs in children, young adults
- Males outnumber females 3:1 until puberty, then equal occurrence
- Self limiting, but high morbidity during course of the disease
Vernal Keratoconjunctivitis

- 50% of patients have some corneal involvement
- Inflammatory cells create white spots at limbus (Horner-Trantas dots)
- Shield ulcers
  - Sterile, result from release of toxic inflammatory mediators, enzymes
  - May cause permanent vision reduction
- 9% have keratoconus

Horners-Trantas Dots

V VKC Pathogenesis
Type I (immediate) reaction

- Increased numbers of degranulated mast cells
  - Elevated tear levels of tryptase, IgE-9
  - Tear histamine may be 10x normal
- Reduced histaminase levels!
- Palpebral conjunctival mast cell numbers can exceed 15,000/mm$^3$
  - Normal 5,000/mm$^3$
- Patients report intense itching!
  - BUT....

V VKC Pathogenesis
Type IV (delayed) reaction

- Cell-mediated reactions through T-lymphocyte result in release of:
  - Lymphokines
  - Interleukins and other products
- CD4+ T helper cells & macrophages have been demonstrated in affected eyes
- T-helper cells release lymphokines, activating
  - Eosinophils (IL-5)
  - Mast cells (IL-3)
- Eosinophils plentiful in conjunctival tissue of VKC patients

Bonini S. et al Vernal keratoconjunctivitis Eye 2004

- Despite name, 23% have perennial form at initial presentation
- 16% of patients with initial vernal presentation develop perennial form
- “Cyclosporine A from 0.5% to 2% emulsion in olive oil or castor oil, used four times per day represents a valid alternative to steroids in severe forms of VKC.”
Cetinkaya A. et al *Topical cyclosporine in the management of shield ulcers*  
Cornea, March 2004

- VKC peaks in April & August
- Shield ulcers a common complication
- Treated 4 young males suffering from steroid-resistant shield ulcers with 1% CsA in olive oil
- Achieved excellent results without many of complications associated w/ steroids

Romanowski E et al *Topical cyclosporine A inhibits subepithelial immune infiltrates but also promotes viral shedding in experimental adenovirus models.*  
Cornea January 2005

- Innoculated rabbit eyes with adenovirus 5 (EKC)
- Treated with CsA 2% or 0.5%
- Reduced number, severity of infiltrates
- Prolonged period of viral shedding by 4 days
- Study suggest use of CSA for EKC would increase likelihood of spread

Wittpenn et al AAO 2004  
Meibomian gland dysfunction

- 33 patients with symptomatic meibomian gland dysfunction
- Length of study = 3 months
- Treatments:
  - Topical CsA 0.05% BID
  - Placebo (artificial tears) BID
- Results
  - Cyclosporine significantly improved signs, symptoms of MGD
Cyclosporine Reduced Meibomian Gland Inclusions

<table>
<thead>
<tr>
<th>Mean Number of Meibomian Gland Inclusions, Change from Baseline after 3 Months</th>
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<tbody>
<tr>
<td>Cyclosporine</td>
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<tr>
<td>-13.5</td>
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*P = .001 vs. placebo

Cyclosporine Improved Corneal Health in Patients with MGD

<table>
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<th>Change from Baseline after 3 Months</th>
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<tbody>
<tr>
<td>Fluorescein</td>
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<tr>
<td>Cyclosporine</td>
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<tr>
<td>-1.3</td>
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</table>

*P = .01 vs. placebo

MGD and Cyclosporine A: 2013

- A 3-month prospective, randomized, double-masked trial -70 patients
- CSA 0.05% vs carboxymethylcellulose
- At 3 months improvements in
  - Study group: OSDI, NIBUT, FBUT, lid margin inflammation, MG expressibility, tarsal injection showed significant improvement from baseline group
  - Control group: only the OSDI improved

Conclusions: CSA & MGD

- CsA statistically superior to placebo
  - Decreased # meibomian gland inclusions
  - Improved fluorescein staining
  - Improved TIBUT
  - Reduced inflammation
  - Increased MG expressibility
- Off-label use of topical CsA appears to be beneficial in treating MGD

Ocular Rosacea

- Wittppen & Schecter. ARVO 2005
  - Improved ocular surface dryness index
  - Improved Schirmer’s scores
  - Improved tear BUT

In our experience, it can be very useful for advanced MGD. It may take months to show efficacy!
Cyclosporine Improved OSDI Scores in Patients with Ocular Rosacea

Mean OSDI Score, Change from Baseline after 3 Months Treatment

- Cyclosporine 0.05%
- Vehicle

Change from Baseline after 3 Months Treatment

- *P = .003 vs. vehicle

Cyclosporine Significantly Improved Schirmer’s Scores in Patients with Ocular Rosacea

Mean Schirmer’s Score (mm/5 min), Change from Baseline after 3 Months Treatment

- Cyclosporine 0.05%
- Vehicle

Change from Baseline after 3 Months Treatment

- *P = .002
- †P = .029 vs. baseline

Tear production was significantly increased vs baseline in the cyclosporine group, decreased in the vehicle group.

Cyclosporine Significantly Improved TBUT in Patients with Ocular Rosacea

Mean TBUT (sec), Change from Baseline after 3 Months Treatment

- Cyclosporine 0.05%
- Vehicle

Change from Baseline after 3 Months Treatment

- *P = .002 vs. baseline

Tear production was significantly increased vs baseline in the cyclosporine group, decreased in the vehicle group.

LASIK

  - Improved outcome of MR with respect to target MR
- Ursea & Schanzlin. ARVO 2005
  - Cyclosporine provided better UCVA Post-LASIK
  - Post-LASIK use of Restasis lowered the enhancement rate from 20% to 10%, a 50% reduction

Proteins in the Eye

- Every protein in our body has a function.
  - Lysozyme: The main protein found in tears; primary function is antimicrobial activity
- Proteins can be found in two states
  - Native State: natural (folded) state
  - Denatured State: forms deposits which bind to the surface of the lens and cause irritation
    - Can be recognized by immune system as “non-self”
    - Can lead to development of GPC
- Cleaner/conditioner can prevent binding of denatured proteins to hydrogel or silicone hydrogel lenses

Protein Deposition on Contact Lenses

Hydrogel Lenses

Denatured state

Cleaner/conditioner can prevent binding of denatured proteins to hydrogel or silicone hydrogel lenses
GPC in Extended Wear Silicone Hydrogels
- This is an OFF LABEL application without literature support…yet
- Start patients on new, clean lenses
- Prescribe Restasis Q 12 hrs with CL in place
- ADVISE the patient that this is off label- you may want to get release
- Tell the patient to report redness, pain, blurred vision immediately

- Myasthenia gravis- most common disease that affects neuromuscular junction
- Autoimmune disorder reduce the number of available postsynaptic ACH receptor
- Cyclosporine now a potential tx without the SE of other meds

Conclusion
- Restasis is:
  - A potent immunomodulator
  - An effective means of treating some forms of dry eye
  - Useful for treating other inflammatory ocular diseases
  - Helpful in enhancing the outcome of refractive surgery

Off Label Use of Restasis
- Allows us to reduce inflammation w/o complications of steroids
- Need to understand the mechanism of action
- Always inform patient use is off-label
- New topical drugs with a similar mechanism of action, but possibly better efficacy in the “pipeline”
  - Eledil- topical pimecrolimus