Off-Label Use
of Cyclosporine in Eye Care
COPE 37858-PH

William Townsend, OD
Incredibly powerful

Immune-free from threat

Exists to detect & destroy invaders

Prehistoric focus – parasites

Major histocompatibility complex (MHC) differentiates “self” from invaders, tumors

Prevents attacking own tissue

“Auto-immunity” genetic disposition to fail to identify self
Lymphocytes and Immunology

- Part of vertebrate immune system
  - Large granular (natural killer cells) lymphocytes
    - Target any cell that does not display major histocompatibility factors (MHC)
  - Examples: tumor cells & infected cells
- Small lymphocytes
  - T cells (mature in thymus)
  - Regulate cell-mediated immunity
  - B cell (mature in bone marrow)
  - Mediate humoral immunity (antibody)

B-Lymphocytes On The Attack!

- Recognize “non-self” antigens
- B lymphocyte differentiate into plasma cell
  - Produce antibodies (lots)
  - Direct action on cell
  - Attract phagocytes
  - Activate complement system
    - Perforates cell wall to release contents
    - Not affected by cyclosporine A

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 release toxic substances- directly kill
  - Viral-infected cells
  - Tumor cells
  - 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

OD   OS
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

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
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
Do you prescribe off-label medications? 

1. Once in a while
2. Once a week
3. Once a month
4. Never
5. On Wednesdays

Tracy’s Shield Ulcer
Pre  Post

Tracy: Two Months Ago

Off label use of medications is not to be taken lightly!
Going Off Label

- Very common in health care
- Prescriber must:
  - Understand the mechanisms of action of the drug
  - Know the pathophysiology of disease processes & immunologic cells involved
  - Know how to differentiate between a good and 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 Tolypocladium Inflatum Gams
- Reversible immunomodulator of T-lymphocytes
- Blocks CD4+ T-lymphocyte proliferation
- Inhibits activation of eosinophils and mast cells

NFAT: nuclear factor of activated T-cells
MAPK: Mitogen-activated protein kinase
NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells
Calcineurin: activates nuclear factor of activated T cell
T-lymphocytes

- Leukocytes produced in bone marrow & 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
Eosinophils: Effect on round worms

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

Atopic Dermatitis
Twenty-two patients with AKC refractory to topical steroid treated with cyclosporine 0.05% or placebo. After 4 weeks, CsA-treated group had fewer signs, symptoms, and no adverse effects observed. Conclusion: CsA appears effective in alleviating signs, symptoms of severe AKC.

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 acetate 1% Q 2 hr
  - Lotapredolol 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 (cromolyn sodium)
- 27% have some long-term VA loss

Tacrolimus - (Prograf, Advagraf, Protopic)

- Tacrolimus topical ointment 0.1% Q 12 hrs for dermatitis
- Used to manage severe refractory uveitis after bone marrow transplants
- May cause burning or itching, w/ increased sensitivity to sunlight and heat

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
50% of patients have some corneal involvement
- Shield ulcers
  - Sterile, result from release of toxic inflammatory mediators, enzymes
  - May cause permanent vision reduction
- Nests of inflammatory cells @ limbus appear as white spots (Horner-Trantas dots)
- 9% develop keratoconus
Increased numbers of degranulated mast cells
- Elevated tear levels of tryptase, IgE-9
- Tear histamine may be 10x normal- itching!
- Patients w/ VKC have reduced histaminase levels!
- Palpebral conjunctival mast cell population @
  - Normal @ 5,000/mm³
  - VKC concentration can exceed 15,000/mm³
  - Patients report intense itching!

Cell-mediated response (T-lymphocyte)
- Lymphokines
  - Interleukins and other pro-inflammatory mediators
- T-helper cells release lymphokines, activating
  - Eosinophils (IL-5)
  - Mast cells (IL-3)
- Eosinophils plentiful in conjunctival tissue of VKC patients
- CD4+ T helper cells & macrophages have been demonstrated in affected eyes
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.”

Bonini S. et al Vernal keratoconjunctivitis. Eye 2004

Steroid-Resistant VKC and Cyclosporine
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

Cetinkaya A. et al Topical cyclosporine in the management of shield ulcers. Cornea, March 2004
Inoculated 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 Romanowski E et al. Topical cyclosporine A inhibits subepithelial immune infiltrates but also promotes viral shedding in experimental adenovirus models. Cornea January 2005
Evaluating Meibomian Gland Dysfunction

- Gross evaluation
- Expression
- TBUT (non-preserved or non-invasive)
- Transillumination
- Infrared imaging
- LipiView

Meibomian Gland Transillumination

Does CsA Help 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

Wittpenn et al ARVO 2005 Meibomian gland dysfunction
A 3-month prospective, randomized, double-masked trial - 70 patients
Treated individuals with MGD using CsA 0.05% vs. carboxymethylcellulose
After 3 months of therapy
Study group: improvements from baseline in: OSDI, NIBUT, FBUT, lid margin inflammation, MG expressibility, tarsal injection
Control group: improvements from baseline in OSDI

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

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.


Thygeson’s Superficial Punctate Keratitis
- Originally described in 1950 by Phillips Thygeson
- Clinical features
  - Transient, bilateral disease
  - Coarse corneal epithelial opacities
  - No associated stromal involvement
- Pathophysiology- who knows?
Symptoms, signs
- Ocular irritation, foreign body sensation, pain, photophobia, blurred vision, tearing, and redness

Differential
- Herpes simplex keratitis, sterile infiltrates

Duszak RS. Diagnosis & management of Thysgen's superficial punctate keratitis. Optometry (2007) 78, 333-338
- Antibiotics shown to be ineffective
- Antivirals have had mixed results
- Topical steroids considered first line of treatment
- Topical cyclosporine effective as a first-line treatment
- Fewer side effects than steroids

Conclusion: Restasis Is...
- A potent immunomodulator
- An effective agent for treating some forms of dry eye/ocular surface disease
- 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

Thank You