Women of Vision Present Are We at Risk for Vision Morbidity

Louise Sclafani O.D.
Co-instructors: Jill Autry, OD, Melissa Barnett, OD, Susan Cotter, OD, Diana Shechtman, OD

GOALS
• Our panel will take on this challenge and discuss this population as it relates to the following conditions: optic neuritis, OCT evaluation, AMD, nutritional controversy, psychosocial issues, management options with strabismus, ocular concerns for common systemic pharmaceuticals, safety issues with ophthalmic drugs, and the hormonal influence on ocular surface disease.

SUMMARY
• As ODs we need to place a higher priority on those individuals at increased risk for vision-threatening ocular disease. It has been estimated that the female gender represents 23% of all visually compromised individuals due to inherent risk factors and lack of access to healthcare.

MODERATOR
Louise A. Sclafani, OD, FAAO
Associate Professor
University of Chicago Hospital

29 yo white female
CC: Decreased VA OD X few days
PMHx: 5 months pregnant
BVA: 20/30 OD     20/20 OS
Pupils: (-) APD
CF: FTFC OD/OS

Women at Risk: Retinal Issues
Diana Shechtman, OD
[dianashe@nova.edu]
Associate Professor of Optometry at NOVA Southeastern University College of Optometry

CASE PRESENTATION
So why wouldn’t WE (female gender) be stressed out?

It’s a BOY...

Courtesy of Dr. M Rafieetary

Fetus maculopathy???
ICSC (idiopathic central serous chorioretinopathy)
Serous macular detachment due to RBR breakdown
Hyperpermeability at RPE site is associated with choroidal circulation disruption/vascular congestion. Focal leakage but definitive cause is unknown.

Which of the following conditions in Not associated with ICSC?
- Vogt-Koyanagi-Harada syndrome (VKH)
- Cushing’s syndrome
- Lupus
- Organ transplant or conditions requiring use of long-term steroids
- Hypercholesterolemia
- Sleep apnea
- H. Pylori (Helicobacter pylori of the stomach)

Which of the following drugs in Not associated with ICSC?
- Viagra (PDE-5 inhibitor)
- Steroids (any form)
- Anti-VEGF therapy
- Pseudoephedrine (nasal decongestant)
- Cancer medications (i.e., sorafenib)

CSR in women
Quillen et al. Ophthalmology Jan 103: 72-9
- 51 women w active CSR divided into 3 groups:
  - Idiopathic, steroid use, pregnancy related
- Results
  - Idiopathic:
    - Clinical findings were similar to those classic MALE
    - These women tended to be OLDER
  - Steroid-related (exogenous) presentation
    - Tended to be bilateral with subretinal fibrin
  - Pregnancy-related
    - Tended to resolve 1-2M s/p delivery

Dxed with possible previous maculopathy 2 yrs ago

ICSC
Idiopathic central serous chorioretinopathy
- Acute
- Unilateral
- Young (20-45)
  - ~30yo
- Type A personality

A Males DISEASE???
F:M 2:10

Clinical characteristic of CSC in females
Retrospective study on 78 women w ICSC
- Results
  - 62% had spontaneous COMPLETE recovery within 5M. Longer resolution was associated with:
    - Increase age & KU forations
  - Final VA in 88% >20/40 & more likely associated:
    - Lack subretinal precipitates & a single presentation
  - (+) factors associated with COMPLETE recovery included:
    - No HTN, no recurrence, duration <5M, no subretinal precipitates

The women with ICSC
- Tends to me OLDER
  - Late 40s-early 50s
- Subretinal precipitates are noted in 30-50% of cases
- Like in MALES, spontaneous resolution & visual recovery >20/40 is common (78-88% of women)
  - Yet, Spaide reported that men and women older than 50 with CSC were more likely to have lower vision and diffuse RPE decompensating at presentation.
In older patients with CSC, it is important to consider the possibility of age-related macular degeneration or idiopathic CNV.

Use of diagnostic modalities
- FA
- FAF
- OCT

The classic Dx modality
Pooling dye

Pooling dye

The Classic FA
But how many pts have it

The value of OCT in the management of ICSC in 2011

OCT or FA may be required to identify absence of possible CNV.

As it resolve...OCT images

The Classic FA

Pooling dye

The Classic FA

Pooling dye
Pt withrix of recurrence
20-50% will have at least one recurrence
Within the yr Associated with “sick” RPE

Within the yr Associated with “sick” RPE

OCT on chronic (>3-6M) or recurrent case may show this

EDI…may explain recurrence

Choroidal thickness at Site of ICSC, which correspond to fFN dye leakage
Decreased vision longstanding

54 WF

Decreased vision longstanding

Another dx modality: FAF
Chronic cases have more widespread decompensating RPE (Diffuse Retinal Pigment Epitheliopathy: Variant of ICSC) May be associated with worse prognosis than TYPICAL presentation. Cases may benefit from PDT...may be seen in FEMALES

**So when to refer?**

1. 68 yf 20/50 (visual disturbances)

A CHRONIC (persistent for 1M or recurrent)

**Laser still commonly implemented when tx is required**

- PDT works on chronic cases
- Note that 3% of pts can experience LONG term severe permanent VL due to complications on photoreceptors

**So what’s the best management?**

A. Observation (60% recover w/i 4-8 wks with good outcomes)
B. Laser photocoagulation
C. PDT
D. Anti-VEGF therapy
E. ASA

**Controversies**

- Increased Calcium required
- High dose Vit A is associated with hip fractures in the elderly because
- Shouldn’t supplement Lutein & beta-carotene together because
- Affects on liver/kidney have to be considered

Referral: Doesn’t follow typical natural hr, visual needs, recurrent

**WOMEN & AMD**

- Who is MORE at risk for AMD: Female or males?
- Is there a correlation b/t MPOD & gender?
Vitamin D
Women lose Vit D as they AGE
• Increased Vit D consumption leads to less (severe) AMD
  — Monozygotic twin study w asym. AMD: those w
  less severe AMD had more Vit D intake: 200 vs
  170 IU
  • Seddon et al. Ophthalmology. 2011;118:1386–1394
• Higher 25OH-VitD leads to less AMD
  — highest vs lowest quintile in <75yo WOMEN

Hormones
• Hormone change during menopause could w DES
• Thought ex hormone replacement therapy (SHRT) may relieve DES
• Epidemiologic studies indicate DES incidence in women on SHRT is
  greater than women not on SHRT
• Specifically, higher incidence of DES of older women on SHRT,
  especially using estrogen alone
• With longer SHRT use, DES frequency and symptomology increased
• Findings disagree with other studies
  — Menopause found to be a risk factor for DES, but SHRT was instead
  some benefit
• Other studies show estrogen therapy in women triggered or
  worsened DES and of Sjogren’s syndrome

Vitamin B complex and relationship to AMD
7.3% f/u w 5,445 women
Treatment group:
  folic acid (2.5 mg/d)
  vitamin B6 (50 mg/d)
  vitamin B12 (1 mg/d)
Rx grp had a lower AMD association
5/21/2014

Prevalence of Dry Eye Disease
• An estimated 25 million Americans report suffering from dry eye.
• 12.76 million postmenopausal women
• 3 million men age 65 and older

Dry Eye Syndrome
• Dry eye syndrome
• Prevalence is much higher among women
• Aging is a risk factor
• Sex hormones are key factors
• Changing hormone levels / decreased androgens are contributory

SHRT
• Theory for conflicting conclusions
• Outcome of SHRT depends on
  1. Estrogen dosage
  2. Age of the individuals when therapy is first initiated
  • Estrogen may only benefit younger women
  • Estrogen detrimental and / or pro-inflammatory in
    postmenopausal women
  3. Type and combination of SHRT applied
  • Estrogen at physiological doses support of lacrimal gland
    function and preservation of anterior ocular surface health at early
    age
  • A higher dose and / or in combination with other hormonal
    supplements would be harmful and / or induce inflammation
  • Elderly women would be more susceptible

Melissa Barnett, OD, FAAO
Department of Ophthalmology & Vision Science
University of California, Davis
Hormone Influence on Ocular Surface Disease

Hormones and Dry Eye
• Ocular surface homeostasis is altered by hormone changes
• Androgens impact structure and function of meibomian and lacrimal
  glands
• Androgen deficiency is associated with the etiology of dry eye
• Mechanisms of why androgens are protective for the ocular surface are
  not well understood
• Sex hormones influence the immune system, suggesting that estrogens
  may modulate a cascade of inflammatory events, which underlie dry eye

The great debate:
do you recommend O3 for AMD
Particular women prone to DES
Best to be selective in choosing the RIGHT pt
Average results may not apply to the individual pt
Systemic Medications May Induce Dry Eye

- Systemic drugs may cause dry eye secondary to:
  - Decreased tear production
  - Alteration of nerve input including reflex secretion and decreased corneal sensation or a direct inflammatory effect on secretory glands.
- May cause increased evaporation by changes in tear film composition, ocular surface abnormalities, number and quality of blinking, changes in mucus producing cells, and inflammatory changes in various ocular tissues.

Thyroid Disease

- Lacrimal glands
- Larger than controls in patients with DES and thyroid disease
- Biopsies of salivary glands
- Infiltrating lymphocytes (mainly CD3+T) with a CD4+/CD8+ (ratio 2:1)
- Activation markers
- Human leukocyte antigen (HLA) class II molecules
- Interleukin (IL)-2 receptor (CD25)

Thyroid Disease

- Thyroid gland – butterfly-shaped endocrine gland
- Located in the lower front of the neck
- The thyroid makes thyroid hormones
- Secretes into blood and carried to every tissue in the body
- Thyroid hormone helps the body use energy, stay warm and keep the brain, heart, muscles, and other organs working as they should.

Thyroid Testing

- Thyroxine (T4 – contains four iodine atoms)
- Major thyroid hormone secreted by thyroid gland
- Amount of T4 produced by thyroid gland controlled by TSH
- Thyroid stimulating hormone (TSH)
- High TSH indicates thyroid gland failing due to problem directly affecting the thyroid (primary hypothyroidism)
- Low TSH indicates that person with an overactive thyroid is producing too much thyroid hormone (hyperthyroidism)

Thyroid Treatment

- Thyroid hormone replacement
- Iodine suppression
- Immunomodulators
- Local radiotherapy
- Orbital decompression
- Oral corticosteroids
Thyroid Treatment

- Difficult to determine in literature if treatments contribute to dry eye development and / or progression
- No clinical trials
- 9 years follow up
- Patients received treatment for Graves' ophthalmopathy
- 25% DED

New Treatment Option

- Methotrexate for the treatment of thyroid eye disease (TED)
- 36 consecutive patients with active TED
- Previously treated with corticosteroids but stopped due to side effects
- Two different weekly doses depending patient weight (7.5 mg or 10 mg)
- Evaluated retrospectively at 3, 6, and 12 months, compared with baseline
- Clinical activity score (7-CAS) – Statistically significant improvement
- Visual acuity (VA) – no significant change
- Ocular motility – improvement
- Eyelid position - no significant change
- May be considered an alternative treatment with TED who cannot tolerate steroids.

Sjögren’s Syndrome

- European-American consensus group
- Two forms of Sjögren’s syndrome
  - Primary Sjögren’s syndrome
  - Secondary: Sjögren’s syndrome
- Aqueous-deficient dry eye
- Dry mouth with the presence of autoantibodies
- Reduced salivary secretion
- Positive focus score on minor salivary gland biopsy
- Monoclonal proliferation of B cells in salivary gland
- All characteristic of Primary Sjögren’s syndrome
- Most commonly rheumatoid arthritis
- Nine out of ten patients with Sjögren’s are women.

The Sjö™ In-Office Testing Kit

- Ocular surface disease due to disease of the lacrimal functional unit.
- Numerous mechanisms for lacrimal gland dysfunction.
- Cholinergic blockade from autostimulations to muscarinic acetylcholine receptor 3
- Inhibition of acinar secretion by inflammatory cytokines such as IL-1
- Cytokine-mediated epithelial cell death
- Replacement of acini by lymphocytes

Sjö testing

- Finger prick
- Obtain a blood sample
- Apply sample to the collection card
- Send card to be analyzed

Sjögren’s Syndrome

- Traditional testing
- Autoantibodies as diagnostic markers
  - Anti-Ro / Sjögren’s arthritis
  - Anti-La / Sjögren’s arthritis
  - Anti-nuclear antibodies (ANA)
  - Rheumatoid factor (RF)
- Positive rate in Sjögren’s syndrome
  - Prevalence in 75% of patients with Sjögren’s

Oral testing for Sjögren’s

- Salivary Flow
  - Measures amount of saliva produced over a certain period of time
- Salivary Scintigraphy
  - Nuclear medicine test that measures salivary gland function
- Salivary gland biopsy
  - Typically performed in the lower lip
  - Confirms inflammatory cell (lymphocytic) infiltration of the minor salivary glands.
Sjögren’s

- New research
- Clinically significant ocular surface disease
- May be present with normal tear production and tear volume.
- Inflammatory mediators that cause ocular surface epithelial disease
- Matrix metalloproteinases (MMPs)
  - Increased production of MMP-3 and MMP-9
- Inflammatory cytokines and T helper (Th) cell associated cytokines.

Inflammmady

- If positive, over 40 ng/ml of MMP-9
- MMP-9 is a proteolytic enzyme from stressed epithelial cells on the ocular surface.
- These are cells that have been subjected to dry eye.
- MMP-9 is a non-specific marker of inflammation.
- Does correlate with dry eye, ocular surface disease and some clinical findings.

Ocular Testing

- Inflammadry® (Rapid Pathogen Screening, Sarasota, Fla.)
- Test similar to an at-home pregnancy test.
- Takes a sample of a patient’s tears and gives a positive (ocular surface disease) or negative (no ocular surface disease) result.
- Test takes ten minutes. A red line indicated elevated MMP-9.
- Test is based on a quantifiable value of the amount of matrix metalloproteinase-9 in the tears.

Inflammadry®

- If positive, over 40 ng/ml of MMP-9
- MMP-9 is a proteolytic enzyme from stressed epithelial cells on the ocular surface.
- These are cells that have been subjected to dry eye.
- MMP-9 is a non-specific marker of inflammation.
- Does correlate with dry eye, ocular surface disease and some clinical findings.

Tear Osmolarity

- Measures osmolarity of proteins in tears.
- The TearLab Osmolarity System (TearLab Corporation)
- Sensitive marker for dry eye.
- Increased rates of evaporation lead to a more concentrated tear film (increased osmolarity).
- Both aqueous deficient and evaporative dry eye disease.
- Abnormal tear osmolarity – failure of homeostatic osmolarity regulation

Tear Osmolarity

- Determines tear osmolarity using 60 nanoliter (nL) volumes of tear fluid.
- Collected directly from the eyelid margin.
- Utilizes a temperature-corrected impedance measurement.
- Indirect assessment of osmolarity.
- After applying a non-specific calibration curve, osmolarity is calculated and displayed as a quantitative numerical value.
- Because dry eye disease is bilateral, but sometimes asymmetrical, the higher of the two measurements should be used for diagnosis.
- Osmolarity values above 308 mOsms/L are generally indicative of dry eye disease.

Cyclokat (Nova22007)

- Topical cyclosporine
- 0.1% vs. 0.05% Restasis
- Novel delivery system
- Cationic emulsion of cyclosporine A
- Positively charged emulsion electrostatically adheres to negatively charged epithelial layer of the eye.

Future Treatments

- Anti-inflammatory Drugs and Immunomodulators

Cyclokat (Nova22007)

- Phase III trial
- 6 month, multicenter, randomized, controlled, double-masked trial
- 492 patients moderate to severe dry eye
- Cyclokat daily vs. vehicle
- Statistically significant improvement in fluorescein staining
- Better outcomes in patients with more severe keratitis
- Currently undergoing additional phase III clinical trial in US
<table>
<thead>
<tr>
<th>CyclASol™</th>
<th>Lifitegrast</th>
<th>Rebamipide Ophthalmic Suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cyclosporine 0.05% solution</td>
<td>OPUS – 2 study</td>
<td>Rebamipide ophthalmic suspension (CRC-12755, Otsuka Pharmaceutical)</td>
</tr>
<tr>
<td>Novalis GmbH</td>
<td>Phase 1</td>
<td>New formulation of potassium class antibiotics</td>
</tr>
<tr>
<td>Received US and European patent approval</td>
<td>7/6 patients with moderately symptomatic dry eye</td>
<td>Mucin secretagogue</td>
</tr>
<tr>
<td>Phase 1 studies</td>
<td>Multicenter double masked placebo controlled trial</td>
<td>Oral therapeutic</td>
</tr>
<tr>
<td>Formulate in preservative free and multi dose bottles for DED</td>
<td>12 weeks</td>
<td>- Treated juvenile idiopathic arthritis in humans by increasing macrophage</td>
</tr>
<tr>
<td></td>
<td>Randomized 3:1 to placebo or Lifitegrast ophthalmic solution</td>
<td>- Expressed in Japan for protection of gastric mucosa and for treatment of dry eye</td>
</tr>
<tr>
<td></td>
<td>Lifitegrast did not meet 2 of 15 clinical signs of keratoconjunctivitis</td>
<td>- Enhances mucus secretion to support tear film adhesion and slow tear film break-up time in human and animal studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase 2 Clinical Trials</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resolvins</th>
<th>EGP-437</th>
<th>Rebamipide Ophthalmic Suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolin E1 (RvE1)</td>
<td>Allergenic hypernascent phospholipid solution</td>
<td>New Rebecca (17 weeks)</td>
</tr>
<tr>
<td>New class endogenous immune response mediators</td>
<td>Derived from lipoxigenation of Omega 3 polynsaturated fatty acids, eicosapentaenoic acid, docosahexaenoic acid</td>
<td>DOX examination</td>
</tr>
<tr>
<td>Derived from lipoxigenation of Omega 3 polyunsaturated fatty acids, eicosapentaenoic acid, docosahexaenoic acid</td>
<td>Lipoxigenase drug molecules in small droplets (w) contained on ocular surface</td>
<td>Signs and symptoms of dry eye measured at baseline, weeks 1, 4, and every 3 weeks after 12 weeks</td>
</tr>
</tbody>
</table>
| In animal model (mouse) | May increase mobility of dry molecules and lead to higher concentration of drugs in the tissues | Improvement in all subjective signs and subjective symptoms ( 
| Improved corneal staining and goblet cell density | Phase I study | Objective signs |
| Phase II trial | Preclinical | Pharmacokinetic |
| Dose dependent and statistically significant improvements for dry eye | Dose dependent | Treatment for various conditions |

<table>
<thead>
<tr>
<th>Lifitegrast (SAR 1118)</th>
<th>Future Treatments</th>
<th>Topical Rebamipide for SLK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifitegrast (SARcode BioScience)</td>
<td>Mucin Secretagogues</td>
<td>Retrospective study</td>
</tr>
<tr>
<td>Novel small molecule lymphocyte function-associated antigen-1 (LFA-1) antagonist</td>
<td></td>
<td>Treatment for SLK</td>
</tr>
<tr>
<td>Mechanism</td>
<td></td>
<td>33 eyes from 20 thyroid eye disease patients</td>
</tr>
<tr>
<td>Prevents protein from binding to the cell</td>
<td></td>
<td>7% Rebamipide</td>
</tr>
<tr>
<td>LFA-1 binds to T cells</td>
<td></td>
<td>Measured at baseline and 4 weeks later</td>
</tr>
<tr>
<td>Inhibits T-cell activation and the inflammatory cascade.</td>
<td></td>
<td>- Proportion of absence of SLK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Area and classification of fluorescein staining</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Schirmer I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Tear break up time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Whole blood smears</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Schirmer I, 3 and 4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 eyes – USC completely resolved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other 5 eyes – significant improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No serious adverse effects</td>
</tr>
</tbody>
</table>

### Lifitegrast (SAR 1118)
- Lifitegrast (SARcode BioScience)
- Novel small molecule lymphocyte function-associated antigen-1 (LFA-1) antagonist
- Mechanism
- Prevents protein from binding to the cell
- LFA-1 binds to T cells
- Inhibits T-cell activation and the inflammatory cascade.

### Future Treatments
- Mucin Secretagogues

### Topical Rebamipide for SLK
- Retrospective study
- 33 eyes from 20 thyroid eye disease patients
- 7% Rebamipide
- Measured at baseline and 4 weeks later
- Proportion of absence of SLK
- Area and classification of fluorescein staining
- Schirmer I
- Tear break up time
- Whole blood smear
- Schirmer I, 3 and 4 weeks

### Rebamipide Ophthalmic Suspension
- Rebamipide ophthalmic suspension (CRC-12755, Otsuka Pharmaceutical)
- New formulation of potassium class antibiotics
- Mucin secretagogue
- Oral therapeutic
  - Treated juvenile idiopathic arthritis in humans by increasing macrophage
- Expressed in Japan for protection of gastric mucosa and for treatment of dry eye
- Enhances mucus secretion to support tear film adhesion and slow tear film break-up time in human and animal studies
- Phase 2 Clinical Trials

### Resolvins
- Resolvin E1 (RvE1)
- New class endogenous immune response mediators
  - Derived from lipoxigenation of Omega 3 polyunsaturated fatty acids, eicosapentaenoic acid, docosahexaenoic acid
- In animal model (mouse)
  - Improved corneal staining and goblet cell density
  - Phase II trial
  - Dose dependent and statistically significant improvements for dry eye

### EGP-437
- Allergenic hypernascent phospholipid solution
- Derived from lipoxigenation of Omega 3 polynsaturated fatty acids, eicosapentaenoic acid, docosahexaenoic acid
- Lipoxigenase drug molecules in small droplets (w) contained on ocular surface
  - May increase mobility of dry molecules and lead to higher concentration of drugs in the tissues
- Phase I study
  - Preclinical
  - Dose dependent
  - Inhibits T-cell activation and the inflammatory cascade. |
Diquafosol Tetrasodium
- Mucin secretagogue
- Topical P2Y2 receptor agonist
- Activation of Gq protein-coupled P2Y2 receptor results in nonglandular secretion of mucin and water
- Potentiates secretions in conjunctival goblet cells
- Stimulates lipid production from meibocytes
- Phase II and III studies
- Topical diquafosol 1% and 3%
- Dose-dependent improvements in ocular surface staining
- 3% more effective than 1%
- Improvements in staining maintained for 52 weeks
- Phase II and III studies
- Topical diquafosol 1% and 3%
- Dose-dependent improvements in ocular surface staining
- 3% more effective than 1%
- Improvements in staining maintained for 52 weeks

Anti-inflammatory Antibiotics
- Topical tetracyclines formulations are being studied
- Tetracyclines effective due to anti-inflammatory and lipid-regulating properties
- Anti-inflammatory by inhibition of activation of MAPK, MMPs, cytokines, lymphocytes and neutrophils
- Liposomal-bound topical doxycycline may increase bioavailability of doxycycline
- Topical azithromycin 1% effective to treat DED associated with blepharitis and contact lens wear
- Additional studies needed

ASED
- Studies
- ASED more effective than artificial tears
- Improved TRUT, corneal staining, symptoms
- From the patients’ point of view, the positive effect of ASED decreased with time.
- Concern about the risk microbial growth
- Concern about high protein content in ASED, which increases risk of microbial growth

Future Treatments
Ocular Lubricants

Sodium Hyaluronate
- Hyaluronic acid
- Help DED by increasing ocular surface wettability
- Improve tear film stability
- Phase II/III studies
- More effective than carboxymethylcellulose to improve DED
- Hypotonic 0.18% sodium hyaluronate drop
- Statistically significant improvement in symptoms and signs of DED

ASED
- Studies
- ASED more effective than artificial tears
- Improved TRUT, corneal staining, symptoms
- From the patients’ point of view, the positive effect of ASED decreased with time.
- Concern about the risk microbial growth
- Concern about high protein content in ASED, which increases risk of microbial growth

AutoLogous Serum Eye Drops (ASED)
- Tear components not found in artificial tear products
- Epidermal-growth factor (EGF)
- Fibronectin
- Vitamin A
- All support the proliferation, maturation, migration and differentiation of corneal and conjunctival epithelia.
- Serum contains IgG, lysozymes and complement, which have bacteriostatic properties.

ASED Cost
- Cost for blood draw and a three-month supply of ASEDs is $300.
- Average annual direct cost approximates $1,200 dollars.

ASED Cost
- Cost for blood draw and a three-month supply of ASEDs is $300.
- Average annual direct cost approximates $1,200 dollars.

Homeopathic Treatment – Ingredients
- Alumina HPUS 1X: Indicated for dryness of the eyes and other mucous membranes due to lack of aqueous secretion, “Sjogren’s Syndrome”.
- Arsenicum album HPUS 12X: Indicated for severe dryness due to inflammation and irritation.
- Nux vomica HPUS 6X: Nux m. is the main remedy indicated for severe aqueous deficiency such as with Sjogren’s Syndrome.
- Zincum met HPUS 10X: Indicated for extreme dryness, inflammation and burning.
- Euphrasia (Eyebright) HPUS 5X: Eyebright is often referred to as a “tonic for the eyes,” and is indicated for inflammation of the conjunctiva, cornea and lids, including melibian glands. Symptoms include redness, dryness, lachrymation and burning of the lid margin.
**Homeopathic Treatment**
- Oral Pellets
- Same ingredients as the eye drops.
- Higher potency.
- Oral form.
- May be used in conjunction with the drops to increase effectiveness by applying dual administration routes with multiple potencies.
- One to three pellets two times per day.

**Rituximab**
- Monoclonal antibody directed against CD 20
- Targets B cells
- B cell depleting
- Studied for systemic manifestations Sjögren’s
- Less known about treatment KCS
- Demonstrates short term benefit
- Suggest B cell targeted therapies potential treatment for KCS

**Future Treatments for Sjögren’s**
- Stimulate tear production with
  - Pilocarpine
  - Diquafosol
  - Approved for treatment in Japan

**Gene Therapy**
- Promising approach for targeted and long-term management
- Advantage to avoid multiple eyedrops daily
- Gene therapy
  - Gene introduced into organ of choice by viral vector
  - In mouse models some success for dry eye
  - Target lacrimal gland and corneal epithelium
  - Treatment well tolerated
  - Improvement in inflammation
  - Improvement in tear production

**EBI-005**
- Phase II/III clinical trial study
- Double-masked, multi-center, randomized, placebo-controlled study
- Evaluate two doses of EBI-005 over 6 weeks in subjects with DED
- 74 subjects
- Multiple centers throughout the United States
- EBI-005 compared to vehicle control
- OSD and corneal fluorescein staining
- Greater improvement in signs and symptoms in EBI-005 treated group compared to vehicle treated subjects.
- Statistically significant improvements in signs and symptoms of DED dry eye disease in the EBI-005 treated subjects compared to baseline

**Cevimeline**
- Activates M3 receptors
- Used to treat xerostomia (dry mouth) in patients with Sjögren’s
- Study to evaluate efficacy of cevimeline in KCS
- Cevimeline improved Schirmer’s, rose Bengal staining, fluorescein staining, TBUT
- Improved patients symptoms
- Side effects:
  - Nausea, abdominal pain, sweating, headache, dizziness, cardiac arrhythmia
- Withdrawal rate 14.1%

**EBI-005**
- Eleven Biotherapeutics (EBI-005)
- First Interleukin-1 inhibitor
- Treat DED or severe allergic conjunctivitis
- Statistically significant improvements in signs and symptoms of DED compared to baseline.
- EBI-005 was generally safe and well tolerated.

**MIM-D3**
- MIM-D3 first in a class of molecules called TrkA agonists.
- Stimulates mucin production
- May have additional benefits
  - Potential to improve visual function
  - May improve corneal sensitivity, and integrity
**Summary**

- Adult strabismus, whether recent-onset or longstanding, compromises binocular function, can cause diplopia and other symptoms, and is associated with wide-ranging effects on various aspects of women’s lives, particularly psychosocial functioning. An overview of psychosocial issues and management options for women with strabismus will be presented.

**Types of Patients**

- Childhood onset

---

**MIM-D3**

- Phase 2 study
- Two-center, randomized, double-masked, placebo-controlled study
- 150 subjects DED
- Randomized 1:1:1 for 1% MIM-D3, 5% MIM-D3 and placebo
- Dosed twice daily for 28 days
- Statistically significant improvements signs and symptoms of DED
- Improvements in ocular staining 2 weeks after treatment.
- Safe and well-tolerated
- Mild ocular adverse events

**MIM-D3**

- Phase III
- 400 patients
- Patients will be randomized to receive 1% MIM-D3 ophthalmic solution or placebo
- Twice daily for 8 weeks
- Primary endpoints
- Corneal fluorescein staining score
- Ocular dryness
- Safety and comfort of MIM-D3 compared to placebo

**Spectrum of Patient Concerns**

- Function
  - Diplopia
  - Visual confusion
  - Poor stereopsis
- Anomalous head posture

**Types of Patients**

- Adult onset
  - CNP 3, 4, 6
  - Divergence Insufficiency ET
  - KT new or consecutive
  - Graves Disease, myasthenia gravis, MS, trauma, CNS issues

---

**Adult Strabismus – Scope of the Problem**

Susan A. Cotter, O.D., M.S., F.A.A.O

Professor of Optometry

Southern California College of Optometry

---

**Spectrum of Patient Concerns**

- Psychosocial concerns – Quality of Life
- Social anxiety
- Social Avoidance
- Employment/promotion
- Headhunters
- Military
- Dating – finding a partner

---

**Clinical Evaluation**

- Eye Alignment: Cover testing at distance and near and different positions of gaze
- Sensory Fusion
  - Correspondence
  - Second-degree fusion
  - Stereopsis
- Motor Fusion
### J.Sjögren’s Syndrome and Testing
- Inflammatory disorder often in association with other autoimmune diseases
- Classically consists of a triad of conditions:
  - Rheumatoid arthritis
  - Dry eye syndrome
  - Dry mouth
- Up to 3 million Americans; Women: Men 8:1
- Often misdiagnosed or underdiagnosed for an average of 5 years
- Untreated cases can lead to worsening symptoms, lung disease, and even lymphoma

### MEDICATIONS AND THEIR EFFECT ON WOMEN
**Jill C. Autry, O.D., R.Ph**
Eye Center of Texas

<table>
<thead>
<tr>
<th>MEDICATIONS</th>
<th>EFFECT ON WOMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure pills</td>
<td>• Dilatation</td>
</tr>
<tr>
<td>• Beta-blockers</td>
<td></td>
</tr>
<tr>
<td>• Birth control pills</td>
<td></td>
</tr>
<tr>
<td>• Hormone replacement</td>
<td></td>
</tr>
<tr>
<td>• Antihistamines</td>
<td></td>
</tr>
<tr>
<td>• Decongestants</td>
<td></td>
</tr>
<tr>
<td>• Antidepressants</td>
<td></td>
</tr>
<tr>
<td>Chemotherapeutic medications</td>
<td>• Topical preservatives</td>
</tr>
<tr>
<td>• Accutane</td>
<td></td>
</tr>
<tr>
<td>• Retin-A</td>
<td></td>
</tr>
<tr>
<td>• Lycer medications</td>
<td></td>
</tr>
</tbody>
</table>

### Which Meds Cause Dry Eye?
- **Blood pressure pills**
  - Beta-blockers
- **Birth control pills**
- **Hormone replacement**
  - Antihistamines
  - Decongestants
  - Antidepressants
- **Chemotherapeutic medications**
  - Topical preservatives
  - Accutane
  - Retin-A
  - Lycer medications

### Sjögren’s Syndrome and Testing
- **American-European Consensus Sjögren’s Syndrome Classification Criteria**
- **New diagnosis/management guidelines in 2012**
- **Sjogren’s Syndrome Foundation**
  - www.sjogrens.org

### Sjögren’s Syndrome
- **I. Ocular Symptoms** (at least one)
  - Dry eyes >3 months?
  - Foreign body sensation in the eyes?
  - Use of artificial tears >3x per day?
- **II. Oral Symptoms** (at least one)
  - Dry mouth >3 months?
  - Recurrent or persistently swollen salivary glands?
  - Need liquids to swallow dry foods?
- **III. Ocular Signs** (at least one)
  - Schirmer’s test (without anesthesia) ≤5 mm/5 minutes
  - Positive vital dye staining (van Bijsterveld ≥4)
- **IV. Histopathology**
  - Lip biopsy showing focal lymphocytic sialoadenitis (focus score ≥1 per 4 mm²)
- **V. Oral Signs** (at least one)
  - Unstimulated whole salivary flow (≤1.5 mL in 15 minutes)
  - Abnormal parotid sialography
  - Abnormal salivary scintigraphy
- **VI. Autoantibodies** (at least one)
  - Anti-SSA (Ro) or Anti-SSB (La)

### Medications and the EYE
- More women than men have dry eye
- Hormone factors contribute to dry eye
- Estrogens vs Androgens
- More women have autoimmune diseases putting them at increased risk for dry eye
  - Rheumatoid arthritis
  - Lupus
  - Sarcoid
  - Sjögren’s
- More women use medications associated with causing dry eye
- Blood pressure pills
- Beta-blockers
-Birth control pills
-Hormone replacement
-Antihistamines
-Decongestants
-Antidepressants
-Chemotherapeutic medications
-Topical preservatives
-Accutane
-Retin-A
-Lycer medications

### Restasis® Recommendations
- **BID dosing in most cases—not PRN**
- Severe cases use QID with a steroid initially
- Continue artificial tear use initially
- Burning initially or later as ocular surface heals
- Use before and after contact lenses (15 minutes)
- Persistence with therapy
  - Results are 2-3 months away
  - Discuss long-term therapy
  - May attempt once daily dosing when controlled
  - Mail order (90 day supply); 2 boxes=1 month supply

### TX: CYCLOSPORIN = RESTASIS
- Decrease inflammation in the cornea, conjunctiva, and lacrimal gland
- Increase tear production
- Increase goblet cell density
- Decrease SPK
- Decrease dependence on artificial tears
- Excellent safety profile
  - Cyclosporine undetectable in blood

TX: CYCLOSPORIN = RESTASIS
Tamoxifen®

- Estrogen antagonist
- Indications for treatment of the following cancers:
  - Breast, Ovarian, Pancreatic, Malignant melanoma
- Ocular side effects reported include the following:
  - Corneal opacities
  - White-yellow subepithelial opacities
  - Retinal opacities with and without CME
  - Most severe ocular association with tamoxifen
  - Anterior subcapsular cataracts
  - Optic neuropathy — rare
  - Macular hole — association not fully determined

Topamax™ Ocular side effects

- Acute myopia and 2° angle closure
- Usually within first month of initiation of topamax
- Associated with suprachoroidal effusion resulting in anterior displacement of the lens and iris
- Chronoidal effusion and ciliary body edema
- Initially see up to 6-8 diopters of myopic shift
- Then a secondary angle closure without pupillary block begins to form
- Then IOP starts to increase

Topamax™ Induced Angle Closure

- **TREATMENT**
  - Need to DC med as quick as possible
  - May need taper; consult with prescribing physician
  - **Topical antiglaucoma agents**
  - **Hyperosmotic therapy**
  - May need IV mannitol if IOP cannot be controlled
  - PI will not restore anatomy
  - Not related to pupillary block

Chloroquine/Hydroxychloroquine (Plaquenil) Ocular findings

- **RETINAL CHANGES**
  - Early changes
    - Retinal pigmented atrophy of RPE
  - Late changes
    - Bull’s eye macular edema
    - Chronic filling defects in FA
  - Distorted color vision
  - Increased risk of retinopathy:
    - > 5 years use
    - Cumulative dose > 1000 g
    - Elderly
    - Kidney or liver disease
    - Concurrent retinal/macular disease

Plaquenil™ Hydroxychloroquine

- Indications:
  - Malaria
  - Rheumatoid arthritis
  - Acute effects on metabolism of retinal cells
  - Ocular side effects:
    - Bilateral ring of RPE depigmentation sparing the fovea
    - With vision threatening loss of macular function

Pseudotumor Cerebri

- Papilledema
- Negative MRI of Brain
- Negative MRV of Brain
- Increased opening pressure on lumbar puncture
- Normal CSF composition
- Obese females (Diamox and weight loss)
- Pregnancy (Diamox after 20 weeks gestation)
- Medication induced (remove offending agent)
MEDICATION INDUCED PSEUDOTUMOR
• Accutane
• Steroids
• Vitamin A
• Tetracycline
• Doxycycline
• Minocycline
• Amiodarone

STERIOD SIDE EFFECTS
• Increased intraocular pressure
  - Topical will increase in 3-4 weeks
  - Oral/IV can increase within 3-4 days
• Cataract
  - Usually posterior subcapsular
• Steroid induced diabetes/decrease control
• Adrenal suppression
• Reduced immunity/infections
• Mood swings/erratic behavior

PREGNANCY
• Medication Dosing
  - Shortest course of treatment necessary to eliminate pathology if possible
  - Topical treatment preferred over oral
  - Punctal occlude
  - FDA Pregnancy Categories for Drugs

ETHAMBUTOL (Myambutol)
• Tuberculosis treatment
• Optic nerve toxicity
• Dose related
  - 50% at a dose of 60-100mg/kg/day
  - 5-6% at a dose of 25 mg/kg/day
  - 1% or below 15mg/kg/day
• May continue to lose vision despite discontinuation of meds

AMIODARONE OPTIC NEUROPATHY
• Optic neuropathy secondary to decreased axoplasmic flow
• Resulting optic nerve edema
• Seen within weeks of initiation of drug
• Discontinue use
• Can mimic NAION
  - Visual acuity less affected than NAION
  - Edema takes longer to resolve than NAION

BREASTFEEDING
• Medication Selection
  - Choose medications with the shortest half-life possible.
  - Choose medications with the highest protein-binding ability.
  - Choose medications with the lowest lipid solubility.
  - Choose medications with the lowest oral absorption.

PREGNANCY
• Medication Selection
  - Choose medications from Category A or B if possible
  - Category C if benefit outweighs risk
  - Category D and X should be avoided completely
  - OK to dilate patients for routine examination during pregnancy

BREASTFEEDING
• Medication Dosing
  - Administer single daily-dose medications just before the longest sleep interval for the infant, usually after the bedtime feeding.
  - Breast-feed infant immediately before medication dose when multiple daily doses are needed.
PAIN MANAGEMENT AND PG

- Tylenol #3 (acetaminophen and codeine)
  - OK in pregnancy
  - NO in breastfeeding
- Vicodin (acetaminophen and hydrocodone)
  - OK in pregnancy and breastfeeding

EYE INFECTION AND PG

- Bacterial conjunctivitis/Anterior or Posterior Blepharitis
  - Erythromycin ointment
  - Azasite
- Corneal ulceration or prophylaxis
  - Tobramycin
  - Compound cephalexin
    - Cefazolin (1st gen)
    - Cefadroxil (2nd gen)

DRY EYE TREATMENT AND PG

- Restasis is contraindicated in pregnancy
- Category C
- Consider decreasing CL wear
- Non-preserved artificial tears/gels/ointments
- 90 day plugs; repeat prn
- Stop oral antihistamine if possible

TOPOCAL OPHTHALMIC STEROIDS

- Pregnancy
  - Category C Medications
  - Risk vs. Benefit ratio should be considered
  - Use lowest dosage possible for shortest length of time possible
  - Highest risk would be between 8-11th weeks of pregnancy
  - Punctal occlusion
- Breastfeeding
  - Prednisone and prednisolone both penetrate poorly into breast milk and are safe for short term use

SOF T TISSUE DISEASE AND PG

- Penicillins
  - Augmentin
  - Amoxicillin
- Cephalosporins
  - Cephalexin
  - Cefadroxil
- Azithromycin
  - Z-pack
- Erythromycin
  - 500mg bid
- Category B Topical Antibiotics

ANTI-VIRALS

- Trifluridine—Category C
- Ziran—Category C
- Oral Acyclovir—Category B
- Oral Famciclovir—Category B
- Oral Valacyclovir—Category B

GLAUCOMA AND PG

- Consider:
  - No treatment?
  - IOP often decreases during pregnancy
  - Consider SLT

- Brimonidine
  - Alpha-agonist
  - Category B
  - Discontinue if breastfeeding
  - Effects in infants due to penetration of BBB
  - Reported with infants less than 2 months of age
- Dipivefrin
  - Category B

ORAL ANTIVIRAL DOSING

- Herpes simplex keratitis
  - In place of topical treatment
    - Acyclovir 400mg 5x day x 10 days
    - Famvir® 250mg tid x 7 days
    - Valtrex® 500mg tid x 7 days
  - For prevention of recurrences
    - Acyclovir 400mg qid bid
    - Famvir® 250mg qid
    - Valtrex® 500 qd
GLAUCOMA AND PG

• Prostaglandins
  – Contraindicated at all stages of pregnancy
  – Consider using post-partum
  – PG important during labor
  – Potentially
    ▪ Induce miscarriage
    ▪ Premature labor
• Carbonic Anhydrase Inhibitors
  – Oral is contraindicated in pregnancy
  – Topical preferred if warranted
  – Acetazolamide OK in breastfeeding according to the American Academy of Pediatrics

GLAUCOMA AND PG

Category C Medications

• Beta-blockers
  – OK after first trimester up to one week before delivery
  – OK during lactation according to American Academy of Pediatrics if use lowest dosage possible
• Pilocarpine
  – Considered safe in pregnancy with literature review
  – Breastfeeding unknown

Thank you

lsclafan@bsd.uchicago.edu