Refractory Ocular Surface Disease, Beyond First-line Therapy

Casey Hogan, OD, FAAO
John E. Conto, OD, FAAO
Jennifer Harthan, OD, FAAO
Timothy Wells, MD, MS

Please silence all mobile devices and remove items from chairs so others can sit. Unauthorized recording of this session is prohibited.
Disclosure Statement:

John Conto: None
Casey Hogan: Allergan, CooperVision, Shire, SSF Member & Donor
Jennifer Harthan: Allergan, Contamac, Metro, Shire
Timothy Wells: None
Please remember to complete your session evaluations online.

Tweet about this session using the official meeting hashtag #academy17
WHAT IS SJÖGREN’S?

Casey L. Hogan, OD, FAAO, FSLS
Diplomate, American Board of Optometry
Advance Eyecare Professionals
Chicago Dry Eye Center of Excellence
SJÖGREN’S SYNDROME

I. DEFINE
II. CLASSIFY
III. DIAGNOSIS OF CONDITION
IV. SYSTEMIC AND OCULAR MANAGEMENT UPDATES

*Sjögren’s Syndrome (Pronounced “SHOW-grins”) is a chronic systemic autoimmune disease

*Lymphocytic infiltration of the exocrine glands

*Leading to “Sicca Syndrome”
Prevalence & Demographics

- 1-3% PREVALENCE
- SECOND MOST PREVALENT AUTOIMMUNE DISEASE
- AFFECTS 4 MILLION AMERICANS
- AFFECTS EVERY RACIAL AND ETHNIC GROUP
- HIGHER F:M PREDILECTION 9:1
- AGE OF ONSET 4th-5th DECADES OF LIFE BUT CAN AFFECT ANY AGE

www.sjogrens.org
WHAT IS SJÖGREN’S SYNDROME?

• **Primary Sjögren’s Syndrome (pSS)**
• **Secondary Sjögren’s Syndrome (sSS)** - secondary disease in association with other autoimmune diseases such as SLE, RA, and systemic sclerosis
  – prevalence of sSS is highest in RA patients (20%)

DIAGNOSIS AND CLASSIFICATION

AMERICAN-EUROPEAN CONSENSUS GROUP (AECG)
AMERICAN GROUP OF RHEUMATOLOGY (ACR)
EUROPEAN LEAGUE against RHEUMATISM (EULAR)
SS DIAGNOSIS

AECG 2002-CLINICAL PRACTICE

• Evidence of a systemic autoimmune cause:
  • 1) ocular dryness and (SYMPTOM)
  • 2) oral dryness (SYMPTOM)
  • 3) Positive SS-A or SS-B antibody
  • 4) Reduced Schirmer’s or corneal stain
  • 5) Positive minor salivary gland biopsy (focus score >2)
  • 6) Scintigraphy = reduced salivary flow

* MUST HAVE 4/6

ACR-SICCA-CLINICAL TRIALS

• 1) Positive SS- A/B or ANA >320;
• 2) Ocular Staining Score >3;
• 3) Positive labial gland biopsy: focus score >1

* MUST HAVE 2/3
The 2016 classification criteria for primary Sjogren’s syndrome: what’s new?

Franco Franceschini 1, Ilaria Cavazzana 1, Laura Andreoli 1, 2 and Angela Tincani 1, 2

**BMC Medicine 2017 15:69**
https://doi.org/10.1186/s12916-017-0837-1

**EUROPEAN LEAGUE AGAINST RHEUMATISM (EULAR) 2016 NEW CLASSIFICATION CRITERIA**

• **ACR +AECG COLLABORATION TO DEVELOP THE 2016 ACR/EULAR CLASSIFICATION OF pSS**

MUST HAVE:

• +SALIVARY GLAND BIOPSY
• +SS-A; SS-B EXCLUDED
• RECOGNIZES SYSTEMIC NATURE-EXTRAGLANDULAR DISEASE & B CELL MARKERS
• OCULAR STAIN SCORE =5
CASE REPORT - 60 YO CAUCASIAN FEMALE
OSDI SCORE 33 (SEVERE)
FILAMENTARY KERATITIS

Schirmer’s I 2mm/2mm + MMP-9 + Elevated TearLab + Lissamine Green (LG) Stain
WHEN IS SEROLOGIC TESTING INDICATED?

Association of Dry Eye Tests With Extraocular Signs Among 3514 Participants in the Sjögren's Syndrome International Registry

SEROLOGY-WHAT TO ORDER?

TRADITIONAL SEROLOGY

• Anti-SS-A/Ro, Anti-SS-B/La
• Antinuclear antibody ANA
• Rheumatoid Factor RF
• CBC

PROPRIETARY NOVEL BIOMARKERS

• Salivary protein-1 (SP-1)
• Carbonic anhydrase VI (CA-6)
• Parotid secretory protein (PSP)
B&L Sjö Test

• LabCorp/Quest Diagnostics
• In-office (time consuming)

http://www.bausch.com/ecp/our-products/diagnostics/sjo *Used with Permission
CASE-DIAGNOSIS

- +ANA 1:2560 Speckled Pattern
- +RF
- +SS-A >101 EU/ml (<20)
- +SS- B >108 EU/ml (<50)

Preliminary Dx SLE sSS 8/2017
OTHER ORGANS MAY BE INVOLVED IN 30-71% OF CASES

DOI 10.1186/s12916-017-0837-1
pSS IS A 5-FOLD HIGHER RELATIVE RISK FOR LYMPHOMA

- LIFE TIME RISK 10%
- MALT LYMPHOMA
- RISKS INCLUDE: SALIVARY GLAND ENLARGEMENT, LYMPHADENOPATHY, SPLENOMEGALY, VASCULITIS, CRYOGLOBULINEMIA & GLOMERULONEPHRITIS

Photo credit: emedicine.Medscape.com
SJÖGREN’S SYNDROME FOUNDATION’S CLINICAL PRACTICE GUIDELINES FOR OCULAR MANAGEMENT IN SJÖGREN’S PATIENTS

- ADOPTED FROM DEWS I
- WWW.SJOGRENS.ORG
- DED AQUEOUS DEFICIENCY WITH AND WITHOUT MGD
- SEVERITY LEVELS 1-4
CASE REPORT- AAO 2002 Poster Session

- 24 YEAR OLD CAUCASIAN ICO STUDENT
- H/O CHRONIC DED WITH CL INTOLERANCE X 5 YEARS
- PRESENTED TO ER WITH PROGRESSIVE MUSCLE WEAKNESS X 1 WEEK AND PAIN
- EKG REVEALED VENTRICULAR BIGEMINY, INTRAVENTRICULAR CONDUCTION DELAY, FLAT T WAVES
- SERUM K+ 1.7 mEq/L (Normal 3.5-5.5mEq/L)
- Metabolic Acidosis
- ANA 1:2600
- +SSA
- +SSB

DX: PRIMARY SJÖGREN'S SYNDROME

<table>
<thead>
<tr>
<th>Title</th>
<th>PRIMARY SJÖGREN'S SYNDROME PRESENTING AS HYPOKALEMIC QUADRIPLEGIA AND SEVERE CARDIAC DYSFUNCTION IN ASSOCIATION WITH DISTAL RENAL TUBULAR ACIDOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, Co-Author</td>
<td>Casey Hogan</td>
</tr>
<tr>
<td>Topic</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>2002</td>
</tr>
</tbody>
</table>
TAKE HOME POINTS

• SS IS MULTISYSTEMIC (30-71% OF CASES)
• RISK FOR LYMPHOMA-10% LIFETIME RISK
• NEW GUIDELINES AVAILABLE AT WWW.SJOGRENS.ORG
• UTILIZE LISSAMINE GREEN AND SCHIRMER’S I AS GUIDE FOR SEROLOGY

THANK YOU! CHOGAN6465@AOL.COM
REFERENCES

9. www.sjogrens.org
10. www.robertfoxmd.com
11. www.baush.com
BLOOD-DERIVED AGENTS FOR OCULAR SURFACE DISEASE

John E. Conto, OD, FAAO, ABCMO
Assistant Professor of Ophthalmology and Visual Science
Medical College of Wisconsin
  – 15 patients, age 20-88, all female
  – 8 with Sjogren’s Syndrome
  – 11 patients remained in study and showed marked improvement in signs and symptoms.
INDICATIONS FOR BDA

- Aqueous deficient OSD, level 3
  - Filamentary keratitis
  - Exposure keratitis
  - OSDI greater than 30
- Persistent epithelial defects
- Intolerant to cyclosporine/lifitegrast
- Keratoneuralgia (“pain without stain”)

Ophthalmic Atlas Images by EyeRounds.org, The University of Iowa
ADJUNCTIVE THERAPY

- Non-preserved artificial tears and gels
- Punctum plugs
- Topical anti-inflammatory agents
- Amniotic membranes (PROKERA®, AmbioDisk™)
- Bandage or scleral lenses
- Environmental controls (moisture goggles, humidifiers)
BDA TYPES

• Autologous serum (ASD)
• Allogeneic serum (AGSD)
• Platelet rich plasma (E-PRP)
• Human albumin (HAD)
• Umbilical cord serum (UCS)
AUTOLOGOUS SERUM DROPS (NATURAL TEAR SUPPLEMENTS)

- Biomechanical qualities
  - lubrication
- Hydration
- Similar biochemistry
  - Ph and Osmolarity
  - Albumin
  - Epithelial growth factor
  - Transforming growth factor- beta 1
  - Vitamin A
  - Lysozyme
  - Surface Immunoglobulin A
  - Fibronectin and cytokines

Table 1. Comparison of the biochemical properties of normal human tears and serum

<table>
<thead>
<tr>
<th></th>
<th>Tears</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.4</td>
<td>7.4</td>
</tr>
<tr>
<td>Osmolarity</td>
<td>298</td>
<td>296</td>
</tr>
<tr>
<td>EGF (ng/ml)</td>
<td>0.2-3.0</td>
<td>0.5</td>
</tr>
<tr>
<td>TGF-β (ng/ml)</td>
<td>2-10</td>
<td>6-33</td>
</tr>
<tr>
<td>Vitamin A (mg/ml)</td>
<td>0.02</td>
<td>46</td>
</tr>
<tr>
<td>Lysozyme (mg/ml)</td>
<td>1.4</td>
<td>6</td>
</tr>
<tr>
<td>IgA (μg/ml)</td>
<td>1190</td>
<td>2</td>
</tr>
<tr>
<td>Fibronectin (μg/ml)</td>
<td>21</td>
<td>205</td>
</tr>
</tbody>
</table>

EGF = epithelial growth factor; TGF= transforming growth factor

AVAILABILITY AND COSTS

• legality and informed consent
  – non-FDA approved
  – within scope of provider given established therapy
  – suggest FAQ patient guide

• protocol
  – blood draw by licensed blood processing laboratory
  – serology testing for hepatitis B, C and HIV-1, 2 and syphilis
  – prepared by compounding pharmacy in 20-100% concentration
  – typical batch of 3 month supply in single use 2 ml or 5 ml vials

• application
  – kept frozen until use (3-6 months)
  – typical dosage 1-2 drop QID

• costs
  – varies between $25-100/month USD
  – rarely covered by insurance
<table>
<thead>
<tr>
<th>Production factor</th>
<th>Published variations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting phase</td>
<td>0-2 days</td>
</tr>
<tr>
<td>Centrifugal force</td>
<td>1500 rpm (300 g) to 4000 g (5000 rpm)</td>
</tr>
<tr>
<td>Duration of centrifugation</td>
<td>5-20 minutes</td>
</tr>
<tr>
<td>Dilution</td>
<td>20%, 33%, 50%, or 100%</td>
</tr>
<tr>
<td>Diluent</td>
<td>0.9% NaCl, BSS, 0.5% chloramphenicol eye drops</td>
</tr>
<tr>
<td>Container</td>
<td>1-6 ml in insulin syringe or dropper bottle</td>
</tr>
<tr>
<td>Storage</td>
<td>-20° to +4°C</td>
</tr>
<tr>
<td>Number of daily applications</td>
<td>3 times to hourly rpm= round per minute; g= g force; BSS= balanced salt solution</td>
</tr>
</tbody>
</table>

“TYPICAL” PROCEDURE

1. Blood Draw
2. Centrifuge
3. Serum Collection
4. Packaging
EFFICACY AND SAFETY OF ASD

• Comparison to first-line therapies
  – 50% decrease OSDI versus 20% with other therapies
  – in PED, 60-90% healed within 25 days

• Complications
  – risk of contamination/infection
  – immunoglobulin deposition in cornea stroma

Cornea: December 2014 - Volume 33 - Issue 12 - p 1245–1251
RECURRENT EROSION

Before ASD

20% ASD QID @ 6 weeks
Before ASD

50% ASD QID @ 8 weeks
OCULAR NEURALGIA
“PAIN, NO STAIN”

Before ASD

20% ASD QID @ 12 weeks
PLATELET RICH PLASMA (PRP) (PLASMA RICH IN GROWTH FACTORS (PRGF))

- Mechanism of action same as ASD
- Higher concentration of growth factors (EGF and TGF-β1)
- Tightens the epithelial adhesion complex

http://eyedoc2020.blogspot.com/2016/10/platelet-rich-plasma-prp-for-dry-eyes.html?m=1

ALLOGENEIC ABO-SPECIFIC SERUM

• Used when autologous serum contraindicated
  – Infants
  – Elderly
  – Patients with blood infectious disease
  – Patients with harmful drug metabolites

• Matched by type A, B, AB and O
• Male donors only to avoid HLA and leucocyte-specific antibodies to avoid possible immune complex-mediated inflammation
• Preparation similar to ASD
• Banked and easily prescribed
• Efficacy similar to ASD

http://dx.doi.org/10.1136/bjophthalmol-2012-301668
HUMAN ALBUMIN

- Tear supplement that allows to retain moisture and drug contact time
- Suppresses apoptosis of conjunctival and cornea cells
- Has antioxidant and anti-inflammatory properties
- Commercially available

UMBILICAL CORD SERUM (UCS)

- Derived from umbilical cords of consenting mothers.
- Diluted to 20% concentration.
- Minimal adverse effects on the eye because of reduced immunogenicity.
- Titers of IgM and IgG antibodies are low and anti-A and anti-B antibodies are absent or only weakly detectable in the serum.

https://nextbio.co.za/optiserum-cb/
BDA CONSIDERATIONS

• Useful adjunct in advanced ocular surface disease
• Safe, with minimal complications
• Compounding varies considerably with ASD
• Cost effective
jconto@mcw.edu

Milwaukee Regional Heath Center/Medical College of Wisconsin
WHY ARE SCLERAL LENSES USED IN OSD?

Jennifer Harthan, OD, FAAO
Associate Professor of Optometry
Chief, Cornea/Contact Lens Service
Illinois College of Optometry
SCLERAL LENSES FOR OSD – DEWS II

Dry Eye Disease Management

The Ocular Surface 2017 15, 575-628DOI: (10.1016/j.jtos.2017.05.006)
WHY SCLERAL LENSES FOR OSD?

• Post-lens fluid reservoir continuously bathes the cornea
• Provides a barrier between anterior surface of eye and posterior eyelid
• Protects the corneal epithelium from shear forces during blinking
• May affect biomarkers
• Mitigates symptoms
• Visual rehabilitation

FITTING TIPS

• Larger diameter is often recommended
• Err on the side of more vault
• Lens handling - more time required for OSD

• Front surface and post-lens tear reservoir debris
  – Remove lenses throughout the day
  – Hydra-PEG
  – ‘Squeegee’ surface
  – Supplemental lubrication
Ocular Surface Conditions

- Graft versus Host Disease
- Stevens-Johnson Syndrome
- Exposure Keratopathy
- Neurotrophic Keratopathy
- Keratoconjunctivitis sicca secondary to chronic autoimmune inflammatory diseases (SS, RA)

GVHD, LISSAMINE GREEN STAINING: PRE-LENS WEAR
SCLERAL LENS EVALUATION
LISSAMINE GREEN STAINING: POST-LENS WEAR

The patient is able to wear his lenses comfortably for up to 12 hours per day.
SJÖGREN’S SYNDROME STAINING: PRE-LENS WEAR
LENS FIT
Non-wetting

Post-fit staining
SJÖGREN’S SYNDROME + FILAMENTARY KERATITIS FLUORESCEIN STAINING: PRE-LENSES WEAR
OCULAR SURFACE: POST-PROKERA AND SCLERAL LENS
SS EYEPRINT PRO
EXPOSURE KERATOPATHY
LIMBAL STEM CELL DEFICIENCY
LSCD SCLERAL LENS FITTING
3 MONTH POST-LENS WEAR
REFERENCES


Ogawa Y, Kuwana, M. Dry eye as a major complication of graft-versus-host disease after hematopoietic stem cell transplantation. Cornea 2003 (22) suppl. 1 S19-27.


ADJUNCTIVE SURGICAL THERAPIES
OCULAR SURFACE DISEASE

Timothy Wells, MD, MS
Associate Professor of Ophthalmology and Visual Science
Medical College of Wisconsin
INDICATIONS FOR SURGERY

• Complications
  – Persistent epithelial defects
  – Neurotrophic ulceration

• OSD, level 4
  – Shortening of fornix
  – Cicatricial scarring of conjunctival/symblepharon
TARSORRHAPHY

- Protects ocular surface from exposure and promotes healing—nature’s bandage
  - Temporary placement can be used in situations in which the cornea needs short-term added protection
    - In perforations, combined with conjunctival flap or tissue adhesive
  - Permanent tarsorrhaphy is still necessary for some patients, esp. decompensated patients with CNV palsy
PERMANENT TARSORRHAPHY

Courtesy of Russell S. Gonnering, MD
PERMANENT TARSORRHAPHY

Disadvantages
– Cosmetically disfiguring
– Functionally Disabling
  - May restrict peripheral vision

Techniques:
– Pillar “suspenders”
– Intermarginal adhesion
EYELID MARGIN ANATOMY
PERMANENT PUNCTUM OCCLUSION

• Thermal cautery
  – High temp device

• Conjunctival flap
  – Reversible


https://www.reviewofophthalmology.com/article/a-stepwise-approach-to-treating-osd
AUTOGRAFT SALIVARY GLAND TRANSPLANTATION

- Increases tear mucin layer
- Labial salivary glands

Marinho DR, Burmann TG, Kwitko S. Labial salivary gland transplantation for severe dry eye due to chemical burns and Stevens-Johnson syndrome OPRS 2010 May-Jun;26(3):182-4

http://drjosephtm.blogspot.com/2015/12/transplantation-of-organs-part-2a-basic.html
Ptosis, Compensatory Frontalis Spasm and Dry Eye: A Common Clinical Triad


May 2008 OPRS Letter to the Editor

Patients with vision-compromising mechanical (brow ptosis, dermatochalasis), and/or involutional ptosis

FABS Triad: 1) Chronic frontalis contraction 2) abnormal blink associated with combined orbicularis inhibition and frontalis contraction 3) symptomatic keratopathy of the interpalpebral fissure

- 39 patients identified in chart over 6 years -36/39 improved dry eye symptoms and decreased keratopathy upon SLE following surgery (browplasty, blepharoplasty, blepharoptosis repair), botulinum toxin or a combination

"...increasing the palpebral fissure in a select group of patients may actually serve to improve lid closure and corneal lubrication.”
Ptosis, Compensatory Frontalis Spasm and Dry Eye: A Common Clinical Triad

- Strong clinical interrelationship

- For dry eye and tearing patients, think about underlying ptosis and look for compensatory frontalis spasm
Clinical Findings of Compensatory Frontalis Spasm

- **Eyebrow malposition**
  - Unilateral or bilateral elevation
  - Look under the hairstyle (bangs) of middle age to older women
  - Deceptively normal brow positions

- **Frontalis Facial Spasm**
  - Persists in downgaze
  - Present with eyelid closure

- **Patients are often unaware**
  - Educate
  - Show them a mirror
  - Ask them to squeeze their eyes closed for ~5 seconds and try to open their eyes without substantially raising their forehead.

http://shywmobile.com
Compensatory Frontalis Spasm

- Overt or underlying ptosis
- Abnormal blink/ exposure keratopathy
  - Relax your forehead
  - “Think to blink”
  - “Use your windshield wipers”
- DES/Tearing
  Facial spasm disorder
  - Orbicularis oculi action antagonized by frontalis
  - MGD (seen with CN7)
Clinical Diagnosis for Compensatory Frontalis Spasm

Real condition
Coding?
ICD-10 Diagnosis
G51.8 Other disorders of the facial nerve

G51 Facial nerve disorders
G51.0 Bell’s Palsy
G51.1 Geniculate ganglionitis
G51.2 Melkersson’s syndrome
G51.3 Clonic Hemifacial Spasm
G51.4 Facial Myokymia
G51.8 Other disorders of facial nerve
G51.9 Disorder of facial nerve, unspecified
SURGICAL CONSIDERATIONS

• Consider review of lid function as contributory to dry eye complaints
• Adjunct to preserve ocular surface
• Permanent punctum occlusion lower first
• Salivary transplantation shows promise but limited currently in scope
twells@mcw.edu
THANK YOU!

Please remember to complete your session evaluations online.

Tweet about this session using the official meeting hashtag
#academy17