Sjogren’s Syndrome: an overview

Arthur A.M. Bookman MD FRCPC
Coordinator, Multidisciplinary Sjogren’s Clinic,
University Health Network

Disclosures

• Member Medical Advisory Boards:
  – Eli Lilly Canada Ltd
  – Janssen Pharmaceuticals
• Principle Investigator Clinical Trials:
  – GlaxoSmithKline
  – Novartis
• Chair, Medical Advisory Board, Sjogren’s Society of Canada

What is Sjogren’s Syndrome?

A. The main cause of dry eye and dry mouth?
B. An autoimmune disease causing dry eyes and dry mouth?
C. The presence of parotid and lacrimal enlargement with dry eyes and mouth
D. An autoimmune disease that can cause systemic illness, dry eyes and dry mouth
E. An autoimmune disease that cannot be diagnosed without the finding of dry eyes and mouth

How do you make a diagnosis of Sjogren’s Syndrome?

A. Demonstrate dry eyes with any test that shows poor tear formation
B. Do a blood test to demonstrate autoantibodies
C. Do a minor salivary gland biopsy
D. Demonstrate the existence of predefined criteria
E. Demonstrate dry mouth by collecting saliva

Sjogren’s Syndrome can present with-

A. Shortness of breath
B. Skin rash
C. Joint pain and swelling
D. All of the above
E. B. and C. above

Learning Objectives

1. Be able to recognize true Sjogren’s Syndrome through the 2016 Classification Criteria
2. Be able to describe the mechanisms of water transport through Aquaporin
3. Discuss the focus of therapeutic options for Sjogren’s associated dry eye
4. Be able to list the extraglandular features of Sjogren’s Syndrome
WHAT IS SJOGREN’S SYNDROME?

Sjogren’s Syndrome

- Is an autoimmune disease
- That most prominently causes inflammation and malfunction of the salivary and lacrimal glands
- But also induces a highly overactive immune system
- And causes extra-glandular complications in up to 30% of patients

SJOGREN’S SYNDROME IS DEFINED BY CRITERIA

There have been 3 sets of internationally accepted criteria since 2002. They have cost millions of dollars to develop and test. The latest are the 2016 ACR-EULAR CLASSIFICATION CRITERIA:

2016 ACR-EULAR Classification Criteria for Primary Sjogren’s Syndrome

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A score of ≥ 4 enables a classification as Primary Sjogren’s Syndrome

Shiboski et al. ARTHRITIS & RHEUMATOLOGY Vol. 69, No. 1, January 2017, pp 35–45

2016 ACR-EULAR Classification criteria

Schirmer’s test ≤5mm/5min

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Van Bijsterveld score >4/9
(Rose Bengal or Lissamine Green dye)

Ocular Staining Score: 5/12
Fluorescein for CORNEA (cobalt blue)

OCULAR STAINING SCORE: Lissamine green staining for conjunctiva
Top left = score 0 < 10 discrete individual green dots
Top right = score 1 >10 and <33 green dots
Bottom left = score 2 with 33 to 100 green dots
Bottom right = score 3 >100 individual green dots

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ACR-EULAR Classification criteria

Unstimulated Salivary Flow <1.5ml/15 minutes
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Initiation: Autoantigens

Ro/SSA, La/SSB:
- Assoc with longer disease duration
- Assoc with extraglandular manifestations
- Assoc with higher focus score in MSGs

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Criteria for an adequate biopsy:
- focal lymphocytic sialadenitis,
- specimen size ≥ 4mm²
Ultrasound: expanding role in diagnosis

THE GLAND IS NOT DESTROYED IN SJÖGREN’S SYNDROME
WHY DOES IT STOP WORKING?

AQUAPORIN (AQP) WATER TRANSPORT CHANNELS

AQUAPORIN (AQP) WATER TRANSPORT MOLECULES

SJÖGREN’S SYNDROME: DISTORTED LOCALIZATION
OF AQUAPORINS

Lancet 2001; 358:1875-76

Laboratory Investigation volume 81, pages 143–148 (2001)

WHY DOES THIS HAPPEN?
• ANTIBODIES TO AQUAPORIN (SjS 28%, DEVIC’S DISEASE 100%)
• DISRUPTION FROM INFLAMMATION
• RADIATION

CAN WE RESTORE AQUAPORIN?
• IN MICE – YES
• IN HUMANS …MAYBE


Laboratory Investigation volume 81, pages 143–148 (2001)
RESTORING AQUAPOIRIN MAY ALLOW SALIVA AND TEARS
CURRENT THERAPEUTIC STRATEGIES BEING INVESTIGATED:

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TO WHOM DO THESE CRITERIA APPLY?

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ACR-EULAR Classification Criteria

To whom do these criteria apply?
1. Anyone who answers yes to validated questions for dry eye or mouth
2. Anyone who presents with Systemic Disease that might be explained by Sjogren’s (see ESSDAI)

SJOGREN'S SYNDROME

Diagnosis

I. Ocular symptoms: a positive response to at least one of the following questions:
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

II. Oral symptoms: a positive response to at least one of the following questions:
1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?
2016 ACR-EULAR Classification Criteria

New Concepts:
1. Anti-La in isolation is not a criterion
2. These are not criteria for secondary Sjogren’s Syndrome
3. These criteria can be applied to patients presenting with unexplained systemic disease
4. These criteria define patients for study or clinical trial
5. These are not diagnostic criteria
6. Absence of anti-Ro & -ve Bx = NO SJOGRENS

Sjogren’s Syndrome: consequences of extra-glandular disease

<table>
<thead>
<tr>
<th>System</th>
<th>Multidisciplinary Sjogren’s Clinic (262 patients)</th>
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</thead>
<tbody>
<tr>
<td>Joint Pain</td>
<td>137 (52.3%)</td>
</tr>
<tr>
<td>Raynaud’s</td>
<td>83 (31.8%)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>9 (3%)</td>
</tr>
<tr>
<td>Intrstitial Neph.</td>
<td>18 (6.8%)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>16 (6%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>18 (6.8%)</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>45 (17.9%)</td>
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Rash and Anti-Ro antibody

- seen in Subacute Cutaneous Lupus

Neonatal Lupus Rash and Anti-Ro antibody.....

Congenital Heart Block and Anti-Ro antibody.....
Sjogren’s Syndrome and Pneumonitis (3%)

Sjogren’s Syndrome and Raynaud’s Phenomenon (32%)

Sjogren’s Syndrome and Vasculitis (6%)

Sjogren’s with Non-Hodgkins B-Cell Lymphoma (7%)

Blepharitis

Rx-
• Hot compresses
• Lid Scrubs
• Liposomal Spray

Normal

Blepharitis
LIFITEGRAST (Xiidra®)

Lifitegrast is a lymphocyte function-associated antigen-1 (LFA-1) antagonist that inhibits T-cell–mediated inflammation (an underlying factor in Dry Eye Disease)

It is an ICAM-like adhesion molecule that attaches to LFA-1 on T-cells Preventing them from attaching to ocular epithelium

Xerophthalmia

Steroid Drops
- Best used as initial treatment for distressful dry eye
  - No more than 5-30 days
  - Beware glaucoma

Autologous Serum Drops
20% diluted serum

Management of Xerophthalmia

Moisture Guard Spectacles:

www.dryeyepain.com
Xerophthalmia

Punctal Plugs
- Lower lids;
- add Upper lids

Beware:
- Proper Sizing
- Infection/Loss
- Overflow tearing
  - Schirmer's < 6-7mm/5 min

Cauterization
- Can recannulate

SLK

Superior-Limbic Keratoconjunctivitis

- Upper bulbar Conjunctiva: foldings, hyperemia, redundancy, and filament formation
- Resulting in: Foreign body sensation, photophobia, excessive blinking and ocular burning and pain
- Can be resected

Systemic management

- Prednisone
  - Minimal effect on parotomagly, no effect on xerostomia, exhaustion, xerophthalmia

- Hydroxychloroquine
  - 3 double blind control trials: Ineffective for xerostomia, xerophthalmia, fatigue or most systemic features
  - Helpful for cutaneous vasculitis, arthralgia
Immunosuppression

- No controlled trials for:
  - Cyclophosphamide
  - Methotrexate
  - Mycophenolate
  - Cyclosporin
  May. 25 patients, pbo controlled, 6 months. No benefit.

BIOLOGICS: ‘rituximab’

- Does rituximab work????
  - J.M. Meijer et al. 2010
  - V. Devauchelle-Pensec et al 2014
  - S. Brown et al 2014

<table>
<thead>
<tr>
<th>Title</th>
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<tr>
<td>Reduction of fatigue VAS in Sjögren syndrome with rituximab</td>
<td>17 patients; benefit (p=0.001)</td>
</tr>
<tr>
<td>Effectiveness of Rituximab in SjS</td>
<td>50 patients; UESF &amp; SSF improved x 6 mins</td>
</tr>
<tr>
<td>TEARS (22.4% vs. 9.1%; P &lt; 0.036). Salivary Flow and Parotid U/S improved</td>
<td>120 pts. Failed at 24 wks (2 of 4 VAS scores - Global, Pain, Fatigue, Dryness)</td>
</tr>
<tr>
<td>TRACTISS Salivary Flow improved</td>
<td>133 pts. Failed at 48 wks to dec. VAS fatigue &amp; oral dryness by 30%</td>
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MAYBE WE ARE DOING IT WRONG

- Failure of medication may indicate:
  - Wrong outcome measures
    - Intractible end-organ damage
    - Composite VAS scores
  - Wrong patients
    - Established disease
    - Few extra-glandular variables
  - Wrong targets
    - Reactive BAFF
    - Antigen processing
    - Germinal Centre formation

SO.....WE INVENTED ESSDAI:
The EULAR Sjögren’s Syndrome Disease Activity Index

<table>
<thead>
<tr>
<th>Domain (weight)</th>
<th>Activity level</th>
<th>Activity level</th>
</tr>
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<tbody>
<tr>
<td>Constitutional (3)</td>
<td>0,1,2</td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy(4)</td>
<td>0,1,2,3</td>
<td></td>
</tr>
<tr>
<td>Glandular(2)</td>
<td>0,1,2</td>
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<td>Articular (2)</td>
<td>0,1,2,3</td>
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Ongoing Trials in PSS Listed at “ClinicalTrials.Gov”
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Answer: D

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D. All of the above
E. B. and C. above

Answer: D

CONCLUSIONS

• Sjogren’s Syndrome has been better defined
• Diagnosis is made by criteria
• Criteria now recognize the many patients that present with systemic illness
• Dryness is disproportionate to the pathology in the glands
• Aquaporin distortion may be the explanation that offers hope for more effective therapy for dry eyes & mouth
• New drugs are in trial for systemic disease

THANK YOU