SJOGRENS DISEASE, A MODEL FOR THE MANAGEMENT OF OCULAR SURFACE DISEASE

Bruce Onofrey, OD, RPh, FAAO
Professor, UEI
University of Houston

Key(s) to managing dry eye?

- **1. ASK** and QUANTIFY (SX’s)
- DO YOU HAVE DRY EYE?
- HOW BAD IS IT?

Management of Dry Eye

- How do YOU spell D-R-Y E-Y-E
- (M.O.N.E.Y) both earned and lost
- Ocular surface disease is a serious business
- Chronic condition
- Multiple dry eye factors
- Mild to severe presentations

OCULAR SURFACE DISEASE INDEX (OSDI)

3 question sets

- **First set: Symptoms**
- **Second set: Function**
- **Third set: Environment**
- Scaled from (0) to (4)
- Allows us to quantify and objectify subjective data
**OCULAR SURFACE DISEASE INDEX (OSDI)**

Please answer the following questions by checking the box that best represents your answer. Have you experienced any of the following during the last week?

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Half of the time</th>
<th>Some of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes that are sensitive to light?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Eyes that feel gritty?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred vision?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor vision?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Have problems with your eyes limited you in performing any of the following during the last week:

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Half of the time</th>
<th>Some of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Driving at night?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working with a computer or bank machine (ATM)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watching TV?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Have your eyes felt uncomfortable in any of the following situations during the last week:

<table>
<thead>
<tr>
<th>Situation</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Half of the time</th>
<th>Some of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Windy conditions?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Places or areas with low humidity (very dry)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Areas that are air conditioned?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**OSDI Severity Grading**

Total OSDI Score = (Sum of Score for All Questions Answered) × (25) / (Total # of Questions Answered)

**Key(s) to managing dry eye?**

2. **FIND THE CAUSE:**

**DRY EYE IS A COMPLEX DISEASE!**
Drugs and Dry Eye
-A natural progression of disease-

ACCUTANE USE = DRY EYE

Hold off on the CL’s:
TX as OSD patient

Key(s) to managing dry eye?

- 2. OBJECTIVELY STAGE THE DISEASE (SIGNS)
Key(s) to managing dry eye?

- 3. SELECT THE PROPER TX
- ACUTE VS CHRONIC
- APPROPRIATE FOR TYPE
- STEP THERAPY

Step therapy of dry eye

- DROPS CANNOT HEAL A SICK CORNEA
- PUT AWAY THE FORCEPS

MRS JOHNSON, THIS WON’T HURT A BIT!!

DRY EYE: THE NEW WAY

- Mucomimetic drop/bandage CL?
- OMEGA 3 : DHA / EPA
- Anti-inflammatory: Steroid induction/Cyclosporin A/Xibrom?
- Punctal occlusion
- Evoxac (Sjogrens)

Restasis VS Steroids for OSD

I ♥ RESTASIS

I ♥ FML
Scoper H. Simplex in K.sicca
Patient study

KWESTION?
DOES PUNCTAL OCCLUSION OR CYCLOSPORIN PREVENT RECURRENT DISCIFORM HERPES?

The Sjogrens patient
• Starts with a bad cornea and serious aqueous deficiency
• Acute and chronic disease
• TX?

Results
• Non-treated group: 6-7 months of disease/yr
• TX with EITHER thermal cautery or topical cyclosporin: 1.1 months/yr of active disease
• TX with both: 0.8 months/yr

• Learning point:
  • OSD patients with H. simplex require aggressive management
  • Topical cyclosporin A is safe and effective in H. simplex patients

Sjögren’s Syndrome - Definition

- Sjögren’s syndrome (SS) is defined as an autoimmune disease of the exocrine glands, involving in particular the salivary and lacrimal glands.
- It may occur alone (primary SS), or in association with a variety of connective tissue diseases and autoimmune disorders (secondary SS).
- The spectrum of presentation of the disorder is very broad, ranging from the local consequences of exocrine gland dysfunction to major, life-threatening systemic complications such as vasculitis, and renal or lung involvement.
Sjögren’s Syndrome

- Affects 500,000 to 2 million people in US
- A major women’s health issue
- Of increasingly important in an aging population
- Often overlooked and neglected
- Holds clues for both autoimmunity and cancer

- Dry mouth and dry eyes (oral and ocular sicca)
- Extraglandular manifestations
- Overlap with other diseases
  - Rheumatic: RA, SLE
  - Thyroiditis, primary biliary cirrhosis, multiple sclerosis
  - Hepatitis C
- Lymphoproliferative disorder

Goal-1

Correct therapy depends on correct diagnosis

a) New international criteria
b) Potential pitfalls in diagnosis

Goals-2

Review the use of Topical medications for dry eyes and dry mouth

Primary Sjogren not just eyes and mouth

A systemic autoimmune disease whose characteristic is ocular and salivary involvement, but also includes other organs such as lung (pneumonitis), kidney (interstitial nephritis), and neurological (central and peripheral) and lymphoproliferative features
Sjögren’s Syndrome - Associations

- Rheumatoid arthritis
- Systemic Lupus
- Scleroderma
- Mixed Connective Tissue Disease
- Primary Biliary Cirrhosis
- Myositis
- Vasculitis
- Thyroiditis
- Chronic Active Hepatitis
- Mixed Cryoglobulinaemia

Cutaneous involvement of patients with primary SJS

a) Cutaneous vasculitis
   - SS associated small vessel vasculitis
     - Cryoglobulinaemic vasculitis
     - Urticular vasculitis
   - Other leucocytoclastic vasculitis
   - SS associated medium vessel vasculitis
b) Other cutaneous processes
   - Ro associated, polycyclic, photosensitive cutaneous lesions (SCLE)
   - Erythema nodosum
   - Livedo reticularis
   - Thrombocytopenic purpura
   - Lichen planus
   - Vitiligo
   - Nodular vasculitis
   - Cutaneous amyloidosis
   - Annular granuloma
   - Granulomatous panniculitis

Pulmonary Involvement in primary SjS

- Various studies have recently described the predominance of bronchial/bronchiolar involvement rather than interstitial disease.
- Bronchiolar abnormalities is present in one third of the patients, with a higher frequency of air trapping in lower lobes.
- Small airway disease is the main functional disorder.
- Large and/or small airway disease was the predominant computed tomography scan pattern in more than 50% of patients.

Renal Disease in Patients with primary SjS. Altered Renal Parameters and Renal Biopsies

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Altered renal parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>55/198</td>
<td>28</td>
</tr>
<tr>
<td>Distal RTA</td>
<td>31/237</td>
<td>13</td>
</tr>
<tr>
<td>Low creatinine clearance</td>
<td>29/182</td>
<td>16</td>
</tr>
<tr>
<td><strong>Renal biopsy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubulointerstitial nephritis</td>
<td>16/27</td>
<td>59</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>12/27</td>
<td>44</td>
</tr>
<tr>
<td>Membranoproliferative</td>
<td>6/12</td>
<td>50</td>
</tr>
<tr>
<td>Mesangial proliferative</td>
<td>5/12</td>
<td>42</td>
</tr>
<tr>
<td>Membranous</td>
<td>1/12</td>
<td>8</td>
</tr>
</tbody>
</table>
Central Nervous System Involvement in primary SjS.
Clinical Features recently described

- Multiple sclerosis-like disease
- Myelopathy
  - Acute myelitis
  - Chronic myelopathy
- Central pontine myelinolysis
- Parkinsonism
- Painful tonic/dystonic spasms
- Bell’s palsy
- Optic neuritis
- CNS vasculitis
- CNS T cell lymphoma
- Cerebral amyloid angiopathy

Current Concepts in the Extraglandular Expression of primary SjS (I)

a) Cutaneous involvement
   - Prognostic significance of cryoglobulinaemia and purpura
   - Ro associated, polycyclic/photosensitive lesions (SCLE-like)

b) Pulmonary involvement
   - High frequency of bronchial/bronchiolar disease (30–50%)
   - Insidious and slow progression of pulmonary disease

c) Renal involvement
   - Indolent subclinical course of TIN
   - Demonstration of glomerulonephritis in 44% of pts biopsied
   - Key role of cryoglobulinaemia in SS related GMN

d) Neurological involvement
   - Increased cerebral white matter lesions
   - Insidious course and poor response to treatment of PSN
   - Autonomic disturbances (abnormal responses to CV tests)

Sjögren’s Syndrome: Ocular manifestations

- Foreign body sensation, like sand in eyes
- Inability to tolerate contact lenses
- Redness, ocular fatigue
- Thick mucous strands in the morning
- Objective: Schirmer’s testing, Rose-Bengal staining
- SX of Dry eye THE MOST the most disruptive and annoying SX of Sjogrens
Sjögren’s Syndrome: Oral manifestations

- Dry mouth; carry water bottles, water at bedside
- “Cracker sign”: unable to eat dry food without liquid
- Poor dentition; unable to wear dentures
- Oral candidiasis

Sjogren’s Syndrome - Cervical Dental Caries

Sjogren’s Syndrome - Diffuse Submandibular Salivary Gland Enlargement

Sjogren’s Syndrome - Ascending Salivary Gland Infection
Classified Criteria for Sjögren's Syndrome*

I Ocular symptoms
II Oral symptoms
III Ocular signs
IV Histopathology
V Salivary gland involvement
VI Autoantibodies

*The presence of 4 out of 6 criteria, including 1 objective criterion (histopathology or autoantibodies). Exclusions include HIV infection, lymphoma, GVHD, sarcoidosis.

In addition to dry eyes and dry mouth

These patients have signs and symptoms that affect other parts of their body ranging from obvious manifestation of skin vasculitis to vague symptoms of fatigue and cognitive loss.

Dryness results in the clinical appearance of keratoconjunctivitis sicca (KCS) characteristic of Sjögren’s syndrome.

NOTE: ENVIRONMENTAL /NON-SJOGRENS TENDS TO BE INTERPALPEBRAL

Diagnostic Issues

In the patient with true Sjögren’s

Sjögren’s syndrome

Extent Of Extra glandular Disease

Therapy And Education
Epidemiology of Sjogren’s

1. Predominantly women (9:1) with two ages of median onset
   In the 30’s and 50’s
2. Much of what we call SLE in the older patient is actually Sjogren’s syndrome

What causes Sjogren’s

A combination of Genetic and Environmental Factors
From family and twin studies, approximately 4 genes are required but even then an environmental factor is needed

Genetics

1. Most important is HLA-DR, which correlates closely with ANA and anti-SS-A antibody
2. Genes of B-cell activation similar to SLE patients
Environmental

No single agent identified
Viral candidates may include EBV and coxsackie viruses
Hepatitis C, HIV and HTLV-1 can mimic

Objective-1
Clinical Issues

There is good agreement about diagnosis for the patient with florid symptoms of keratoconjunctivitis sicca (KCS), parotid swelling, and high titer ANA with SS-A/SS-B.
The issue in these patients will be therapy
And the extent of extra glandular involvement.

If you order an MRI

1. Ask for MRI -sialography (this is just a fat suppression view to visualize the ducts). It takes only 5 minutes more and no risk
2. Have the MRI printed out on CD and give copy to patient for their record

Differential Diagnosis: is the Dryness Due to Other Causes

- Non Salivary Gland Disease
  - Drugs-esp., BP and cardiac
  - Muscle relaxants
  - Antidepressants and OTC
  - Antihistamines/decongest.
  - Acute anxiety and depression
  - Mouth breathing
  - Central lesions:
    - Multiple sclerosis
    - Alzheimer’s

- Salivary Gland Disease
  - Hepatitis C
  - Sarcoidosis
  - Fatty Infiltrate of Gland
  - HIV disease
  - Lymphoma
  - Cancer of the Salivary Gland
  - Infection of gland
  - (TBC, Actinomycosis)
  - Head & neck radiotherapy
DX: Autoantibodies in Sjogren’s syndrome

- ANA: ~67%
- Anti Ro/SSA:
  - Recognize cellular proteins with M.W. ~52-60kDa
  - Associated with Sjogren’s (75% primary, 15% secondary), SLE (50%)
  - Subacute cutaneous lupus, neonatal lupus and congenital heartblock
  - 0.1-0.5% normal adults
- Anti-La/SSB:
  - Almost always associated with anti-Ro (except in primary biliary cirrhosis and autoimmune hepatitis)
  - Associated with Sjogren’s (40%), SLE (15%), and neonatal lupus

Anti-Ro/La and Neonatal Lupus Syndromes

- From transplacental passage of maternal anti-Ro/La in the perinatal period
- Transient rash
- Congenital heart block
  - ~1% rate of CHB in Ro +ve mothers
  - ~15% rate of CHB in second child
- most often identified between 18-24 wks gestation
- ~50% of asymptomatic mothers with children who have neonatal lupus will eventually develop an autoimmune disease such as lupus or Sjogren’s

How good are our tests?

The lip biopsy and the ANA and anti-SS A antibody are often considered “specific” tests but they are not specific

Pitfalls in diagnosis-1

A) Positive ANA does not mean Sjogren’s or SLE
   These tests are sensitive but not specific
   (only about 1:100 patients with ANA 1:320 will have SS or SLE)
B) anti SS-A antibody more specific—but differences between detection kits
Even the Gold standard of lip biopsy is often misread by pathologists

On review of outside biopsies diagnosed as Sjogren’s syndrome, over half (32/60) were reclassified on review.


Treatment of Sjögren’s Syndrome

- Ocular manifestations
  - Artificial tears
  - Punctal plugging
  - Topical cyclosporine
- Oral sicca
  - Good dental hygiene
  - Avoid anticholinergic drugs
  - Saliva substitutes
  - Stimulate salivary flow
    - Sugar free candy/gum
    - Muscarinic agonists
  - Treat oral candidiasis
- NSAIDs
- Corticosteroids
- Hydroxychloroquine
- Immunosuppressives e.g. methotrexate, cyclophosphamide

DEFINITION OF Dry Eye (DEW’s) 2007

- 1. Multifactoral disease
- 2. Symptoms:
  - discomfort
  - visual disturbance
- 3. Signs:
  - tear film instability
  - ocular surface damage
  - increased tear osmolarity
  - inflammation of ocular surface

CLINICAL GUIDELINES FOR MANAGEMENT of DRY EYE DISEASE ASSOCIATED with SJOGREN DISEASE

THE OCULAR SURFACE

APRIL 2015
DRY EYE: CATEGORIES

• AQUEOUS DEFICIENT: Sjogrens-the extreme
• EVAPORATIVE: MGD et al.

Prevent Evaporation

• USE MAYONNAISE or something like it
• Refresh ENDURA: OLD
• SOOTHE XP/Systane Balance: NEW

TESTS-NON-INVASIVE

• OBSERVATIONAL TESTS
• CORNEAL LIGHT REFLEX
• TEAR MENISCUS
• MARGINAL TEAR STRIP
• DEBRIS
• FILAMENTS
• FOAM (LATERAL CANTHUS)

TESTS- “INVASIVE”

• TBUT
• RED THREAD
• SCHIRMER 1 AND 2
• OSMOLARITY
DR. ONOFREY-AIN’T ALL ARTIFICIAL TEARS THE SAME?!

CHEAP AND CRAPPY

NOOOOOOOOOO!!!

ART. TEARS DIFFERENTIATION

- ELECTROLYTES: K (+), HCO3(-)
- Prevent surface damage
- BION TEARS (Alcon)
- THERATEARS (AVR/Akorn)

ART. TEARS: OSMOLARITY

- PURPOSE: Lower tear osmolarity
- HypoTears (Novartis)
- Theratears
- Optive (Allergan): glycerin/erythritol/levocarnitine-barrier against cellular dehydration

ART. TEARS: VISCOSITY

- NOTE: THICKER IS NOT BETTER
- PROS: LONGER DURATION
  - CUSHION EFFECT
  - REDUCED TEAR EVAPORATION?
- CONS: GUMMY
  - BLURRY
  - DEBRI ON LIDS
  - GELLING MATERIALS “STEALS” H2O
- Old agents: carboxymethylcellulose/hydroxymethylcellulose
- New stable gel systems: Hydroxypropyl-guar + glycols = stable gels = less corneal desiccation (Alcon Systane)
ART. TEARS: LIPIDS

- THE ANSWER TO DRY EYE-MAYONNAISE = OIL IN WATER EMULSIONS
- MIMIC THE NATURAL TEARS
- CASTOR OIL = REFRESH OPTIVE ADVANCED = THE VEHICLE FOR RESTASIS-CYCLOSPORIN A
- MINERAL OIL = SOOTHE XP/RETAINE MGD
- SYSTANE BALANCE = STABLE GEL + LIPID

ART. TEARS: HYALURONIC ACID

- HYGROSCOPIC = ATTRACTS WATER
- MIMICS THE MUCIN LAYER
- Blink Tears (AMO)
- Blink gel Tears
- Oasis Tears (Oasis medical)
- Oasis Tears Plus

Artificial Tears-A prescription drug???

- FRESKHOTE (Focus labs)
- WHY A PRESCRIPTION?
- PSYCHOLOGICAL EFFECT ON PATIENT AND THE DOC! CHARGE MORE
- PROPRIETARY COMPONENT
- “AMISOL” PHOSPHOLIPID
- PL’S ATTRACTED TO H2O AND LIPIDS-LIKE A SURFACTANT
- HIGH ONCOTIC PRESSUE ALSO ATTRACTS H2O

THE BOTTOM LINE ON AT’S

- 1. NO CLEAR SUPERIORITY
- 2. CONSIDER NEW FORMULATIONS THAT INCORPORATE LIPIDS AND STABLE GELS
- 3. AVOID OLD VISCOSITY AGENTS IN SJOGRENS
- 4. MUST STOP VAPOATION IN SJOGRENS (AQUEOUS DEFICENCY)
- 5. AVOID BAK/EDTA PRESERVATIVES IF GREATER THAN QID DOSING?
LACRISERT

60 inserts = $400.00

STEROIDS/RESTASIS/NSAID’s/PUNCTAL OCCLUSION

• STUDY #1
• STEROIDS BEFORE PUNCTAL OCCLUSION - 2 WEEKS OF TOPICAL STEROIDS BEFORE OCCLUSION = LESS STAINING AND SYMPTOMS

• STUDY #2
• GROUP 1: AT’s ONLY
• GROUP 2: AT’s WITH NSAID’s
• GROUP 3: AT’s WITH STEROID
• GROUP 3 INCREASE IN GOBLET CELLS AND REDUCTION IN INFLAMMATORY CELLS

RESTASIS AND STEROIDS

• RESTASIS SLOW (MIN 8-12 WEEKS TO WORK)
• DOESN’T WORK FOR EVERYONE
• STEROIDS 2-4 WEEKS PRIOR TO RESTASIS = DECREASE IN SYMPTOMS
• PREDICT SUCCESS WITH RESTASIS?

RESTASIS

• “REFRESH ENDURA” IE MAYONNAISE DOES MOST OF THE “HEAVY” LIFTING
• DECREASE IN AT USE WITH RESTASIS-DUHH!
• CYCLOSPORIN INCREASES GOBLET CELL DENSITY
• CYCLOSPORIN REDUCED MEIBOMIAN INSPISSATION
• WORKED BETTER THAN TDEX ST FOR LID DISEASE
### OMEGA 3’s VS 6’s

<table>
<thead>
<tr>
<th>OMEGA 3 =</th>
<th>LINOLEIC ACID, EPA AND DHA AND RESOLVINS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL ANTI-INFLAMMATORY</td>
<td>LESS INFLAMMATION</td>
</tr>
<tr>
<td>LESS MEIBOMIAN VISCOSITY</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OMEGA 6 =</th>
<th>LINOLEIC ACID</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARACHADONIC ACID</td>
<td></td>
</tr>
<tr>
<td>INFLAMMATORY EICOSANOIDs (PROSTAGLANDINS)</td>
<td></td>
</tr>
</tbody>
</table>

**THE SECRETAGOGUES**

<table>
<thead>
<tr>
<th>SALAGEN (PILOCARPINE) 5MG</th>
<th>EVOXAC (CEVIMELENE) 30MG</th>
</tr>
</thead>
<tbody>
<tr>
<td>VERY SHORT ½ LIFE-</td>
<td>PARASYMPATHOMIMETIC</td>
</tr>
<tr>
<td>WHATTTTTTTTTTTT?</td>
<td></td>
</tr>
<tr>
<td>HIGH POTENCY-</td>
<td>UP TO TID</td>
</tr>
<tr>
<td>WHATTTTTTTT?</td>
<td>TITRATION</td>
</tr>
<tr>
<td>UP TO QID</td>
<td>NAUSEA/SWEATING</td>
</tr>
<tr>
<td>10-30MG??</td>
<td>SLUDGE OR 3 D’s</td>
</tr>
<tr>
<td>SWEATING/GI CRAMPING?</td>
<td>SALIVATION</td>
</tr>
<tr>
<td>DRY MOUTH &gt; EYE</td>
<td>DROOL</td>
</tr>
<tr>
<td>OFF-LABEL-EYE</td>
<td>UNRINATION</td>
</tr>
<tr>
<td>BETTER THAN AT’S AND PUNCTAL PLUGS</td>
<td>DEFACATION</td>
</tr>
<tr>
<td></td>
<td>GI ACTIVATION</td>
</tr>
<tr>
<td></td>
<td>EMESIS</td>
</tr>
</tbody>
</table>

---

“Doctor Onofrey, You changed my life”

Oral meds for dry eye?

- Parasympathomimetic
- Better tolerated
- 30mg TID
- No titration necessary—maybe
- NEVER in asthmatics
PUNCTAL OCCLUSION

- IMPROVED TBUT AND SCHIRMER
- ONLY AFTER STEROID/RESTASIS
- PATIENTS PREFER REVERSIBILITY
- PATIENTS HATE EPIPHORA

AUTOLOGOUS SERUM AND BEYOND

- BLOOD CELLS REMOVED
- SERUM USED AS AT’s
- HIGH COST
- INFECTION
- STORAGE TIME
- INCONVENIENT

ALBUMIN

- R-Tech Ueno Complete Phase 1/2 Study of Recombinant Human Serum Albumin-Containing Ophthalmic Solution for Severe Dry Eye - ALBUCUT
- 5% ALBUMIN PRODUCED BY GMP PHARMACY

50CC-THAT’S A LOT OF DROPS
MUCOLYTICS/BANDAGE

- 10% ACETYLCYSTEINE
- Bandage CL-silicone hydrogel

The lids

- Dx and manage lid disease
- Consider tarsorrhaphy or lid weights for exposure disease
- Botulinum for chemical tarsorrhaphy

Sjögren’s Syndrome

Systemic Therapy

Evidence Based Treatment of SjS
A Review of RCTs using the Cochrane Approach

- Since 1978, 34 RTCs (testing 15 different therapeutic modalities) have been published.
- A trend towards larger sample size and improved quality of trials has been observed.
- There is evidence that muscarinic agonists (pilocarpine, cevimeline) and local IFN-α improve glandular function and symptomatology.
- Topical treatment with Cyclosporin eye drops shows anti-inflammatory effects and improves ocular symptoms, but results on tear secretion rate are conflicting.
- Systemic treatment with steroids and antimalarians downregulates markers of immune system activation, without evidence of any short- or long-term clinical benefit.
- Low dose oral azathioprine is ineffective and prone to side effects.

New therapeutic agents for the treatment of patients with primary SjS

<table>
<thead>
<tr>
<th>Biological agents</th>
<th>Dose</th>
<th>Number of patients treated</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infliximab</strong></td>
<td>3 mg/kg ev</td>
<td>4 (SS associated with RA)</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (primary SS + neuropathy)</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 (primary SS)</td>
<td></td>
</tr>
<tr>
<td>86, 87</td>
<td>5 mg/kg ev</td>
<td>54 (primary SS)</td>
<td>90</td>
</tr>
<tr>
<td><strong>Etanercept</strong></td>
<td>25 mg/12 h sc</td>
<td>15 (primary SS)</td>
<td>91</td>
</tr>
<tr>
<td><strong>Rituximab</strong></td>
<td>375 mg/m² ev</td>
<td>1 (primary SS + lymphoma)</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (primary SS + lymphoma)</td>
<td>99</td>
</tr>
<tr>
<td><strong>IFNα</strong></td>
<td>150 IU/8 h po</td>
<td>300 (primary SS)</td>
<td>94</td>
</tr>
</tbody>
</table>

Anti-TNFα Therapy in SjS

△ In a open trial infliximab (3 infusions, 3 mg/kg) showed to improve unstimulated salivary flow and restore the normal aquaporin-5 distribution in minor salivary glands in a small number of patients with SS.

△ In a single centre open pilot study on 15 patients, etanercept (25mg twice weekly during 12 weeks) showed to improve fatigue and reduce ESR and CRP levels. No effects were observed on the function of lacrimal and salivary glands.

THERAPEUTIC GUIDELINES IN SJÖGREN’S SYNDROME

Extraglandular manifestations (1)

1. arthralgias/ arthritis
   - NSAID’s
   - steroids (low dosage)
   - anti-malarians

2. Raynaud’s phenomenon
   - vaso-active drugs (Ca-antagonists)

3. hemocytopenia (usually mild forms)

4. vasculitis (purpura, peripheral neuropathies, etc.)
   - steroids (low/medium dosage)

5. Myositis
   - steroids (high dosage or pulse)
   - MTX or cyclophosphamide (pulse)

6. Interstitial lung involvement (in active phase)
   - steroids (high dosage or pulse)
   - cyclophosphamide (daily dose or pulse)

7. Tubulointerstitial nephritis
   - steroid (medium/high dosage)
   - bicarbonates to correct acidosis in a late phase
8. Fatigue and depression

- Steroids (low dosage) are indicated in the case of late morning or early afternoon fatigue, often associated with flu-like symptoms and probably related to disease activity and production of specific cytokines (IL-1, TNF-α).

- Psychoactive drugs in the case of early morning fatigue, often associated with poor sleep and fibromyalgia symptoms. Benzodiazepine agents to induce sleep and antidepressant drugs lacking anticholinergic effects (fluoxetine, fluvoxamine, etc.) can be tried.