Dry eye disease:
A tear film and ocular surface challenge
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Assignment

• Review the definition, impact, classification, mechanism & risk factors of dry eye disease

• Highlight the new therapeutic approaches and challenges for the treatment of dry eye disease
“Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.”

TFOS DEWS, 2007
Dry Eye Disease

- Afflicts > 40 million people in USA
- Leading cause of patient visits to eye care practitioners
- Has no cure
Global Prevalence of Dry Eye in Adults

- Singapore Malay
- Sumatra
- Taiwan
- Tibet
- Beijing
- Mongolia
- Japanese High School Students
- Japanese VDT users
- US Women's Health Study
- US Male Physicians
- Melbourne
- Blue Mountains (AUS)
- Beaver Dam (US)
- Maryland USA
- Spain

Debra A Schaumberg
2010
Dry eye disease:
Risk factors
Sex Differences in DED Prevalence

Rate Ratio (95% Confidence Interval)

- 50-54: 1.54 (1.26, 1.90)
- 55-59: 2.02 (1.72, 2.36)
- 60-64: 2.28 (1.90, 2.75)
- 65-69: 2.05 (1.71, 2.46)
- 70-74: 1.75 (1.43, 2.14)
- 75+: 1.39 (1.07, 1.77)
- All (crude): 1.57 (1.47, 1.69)
- Standardized: 1.70 (1.54, 1.88)

Prevalence of Dry Eye by Age
Prevalence of Dry Eye in US, by Race

Additional risk factors for DED

- Androgen deficiency
- Estrogen replacement therapy
- Benign prostatic hyperplasia & associated medications
- Hypertension
- Antidepressant medications
Dry eye disease: Quality of life
Dry eye & quality of life

- Impact of moderate to severe dry eye is comparable to dialysis and severe angina
- DED leads to problems with reading, computer use & work performance, and is associated with role limitations, lower vitality & poorer general health
Dry eye disease: Approved treatments
Topical Restasis

“Restasis is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.”
Restasis sales in 2010: > $700 million

“… statistically significant increases in Schirmer wetting of 10 mm versus vehicle…effect was seen in ~ 15% of RESTASIS® ophthalmic emulsion treated patients versus ~ 5% of vehicle treated patients.”
Dry eye disease: Potential treatments
Treatment Targets

- Mucin deficiency
- Aqueous tear deficiency
- Lipid deficiency
- Ocular surface damage
New therapeutic approaches for the treatment of mucin deficiency

- Diquafasol
- Gefarnate
- Eupatilin
- Rebamipide
- Galectin 3
- Tamarind seed
- Trefoil factor family peptide 3 (TFMP3)
- Mycophenolate mofetil
- Nerve growth factor & mimetic
Stimulation of ocular surface mucins

- **Mycophenolate mofetil** – $\uparrow$ MUC5AC in human conjunctiva
- **DA-6034 (Eupatilin)** – $\uparrow$ MUCs 1, 2, 4, 5AC, 5B & 16 in human conjunctiva
- **Rebamipide** – causes mucus secretion (activates cyclooxygenase 2)
- **TFMP3** – stabilizes mucous layer

Gipson IK, IOVS 2007;48:4391-4398
Nerve growth factor & mimetic

- ↑ Goblet cell number & MUC 5AC production
- ↑ Corneal sensitivity
- Promotes corneal epithelial cell wound healing
New approaches for the treatment of aqueous tear deficiency

Immunomodulation
Lacrimal gland stimulation
Lacrimal Gland Stimulants

- TRPV1 receptor modulators
- Taste & salivation
- Anethol trithione
- Uridine
- Hydroxychloroquine
- Vitamin A
- Muscarinic receptor agonists
- Topical androgens
Transient receptor potential vanilloid 1 (TRPV1) receptor modulator

Intranasal application of Civamide, a TRPV1 receptor modulator, reportedly increases tear production. TRPV1 is a permeable, non-selective cation channel.
Increased Schirmer Wetting Score

- **Oral anethole triothine** – a cholagogue
- **Oral uridine** – metabolized into P2Y2 agonist
- **Oral hydroxychloroquine** – in Sjögren’s syndrome patients with α-fodrin antibodies
- **Vitamin A** – retinyl palmitate eye drops
Muscarinic Receptor Agonists

Salagen (M3 agonist, oral pilocarpine)

Cevimeline (M1/M3 agonist)
Oral Pilocarpine and Cevimeline

Sjögren’s Syndrome:

Beneficial effect on subjective eye symptoms

No effect on tear volume

Pilocarpus pennatifolius
New approaches for the treatment of lipid deficiency

LipiFlow & Maskin Intraductal Probe
Azithromycin & IL-1Ra
Topical androgens
Treatment of Meibomian Gland Duct Obstruction

TearScience LipiFlow

Maskin Intraductal Probe
Treatment of Posterior Blepharitis

Azithromycin (Azasite, Azyter)

Interleukin-1 receptor antagonist
Topical androgens: Treatment of meibomian gland dysfunction
Treatment of Ocular Surface Damage

**Immunomodulation**

**Hydration**

**Boundary Lubrication**
Immunomodulation

Omega 3 fatty acids & nutritional foods
Glucocorticoids
NSAIDs
Calcineurin inhibitors
Antibodies & other drugs
Omega 3 fatty acids & nutritional foods

- HEALTHY SWEETS (such as plain dark chocolate) Sparingly
- RED WINE (optional)
  - No more than 1-2 glasses a day
- SUPPLEMENTS
  - Daily
  - TEA (white, green, oolong)
    - 2-4 cups a day
  - HEALTHY HERBS & SPICES (such as garlic, ginger, turmeric, cinnamon)
    - Unlimited amounts
- OTHER SOURCES OF PROTEIN
  - High quality natural cheeses and yogurt, Omega 3 enriched eggs, skinless poultry, lean meats
    - 1-2 a week
- COOKED ASIAN MUSHROOMS
  - Unlimited amounts
- WHOLE SOY FOODS (adzukas, soy nuts, soy milk, tofu, tempeh)
  - 1-2 a day
- FISH & SEAFOOD (wild Alaskan salmon, Alaskan black cod, sardines)
  - 2-6 a week
- HEALTHY FATS (extra virgin olive oil, expeller-pressed canola oil,
  - nuts - especially walnuts, avocados, seeds - including hemp seeds
  - and freshly ground flaxseeds)
  - 5-7 a day
- WHOLE & CRACKED GRAINS
  - 3-5 a day
- PASTA (al dente)
  - 2-3 a week
- BEANS & LEGUMES
  - 1-2 a day
- VEGETABLES (fresh raw and cooked, from all parts of the color spectrum, organic when possible)
  - 4-5 a day minimum
- FRUITS (fresh in season or frozen, organic when possible)
  - 3-4 a day
Glucocorticoids

- EGP-437 – EyeGate Pharma, dexamethasone & transscleral iontophoresis
- Mapracorat – B&L, selective glucocorticoid receptor agonist
- DE-110 – Santen, selective glucocorticoid receptor agonist
- Lotemax – B&L
Possible glucocorticoid side effects

Ocular side effects have included blurred vision, discharge, ocular pain and discomfort, increased intraocular pressure, foreign body sensation, pruritus, and hyperemia in 1% to 5% of patients. Dry eye, tearing, conjunctival and corneal edema, keratitis, photophobia, corneal erosion, corneal ulcer, corneal staining, increased fibrin, tearing, photophobia, edema, irritation, browache, lid margin crusting, and infiltrate have been reported in less than 1% of patients.

In addition, prolonged use of topical ophthalmic corticosteroids has caused ocular hypertension/glaucoma, optic nerve damage, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, and secondary infections of the eye. The use of topical corticosteroids has caused perforation of the globe where there is preexisting thinning of the cornea or sclera.
Non-steroidal anti-inflammatory drugs

Remura (ISTA Pharmaceuticals) & ISV-101 (InSite Vision) – bromfenac, thought to inhibit cyclo-oxygenases 1 & 2
Calcineurin inhibitors

1. Activation of the T-cell receptor results in increased intracellular Ca^{2+}.
2. Activation of calcineurin, a Ca^{2+}-dependent phosphatase.
3. As a result of dephosphorylation by calcineurin, NFATc moves from the cytoplasm to the nucleus.
4. NFATc associates with other nuclear components leading to activation of genes encoding cytokines.
5. Release of IL-2.

 Tacrolimus  Cyclosporine

Calcineurin inhibitors regulate the immune response by inhibiting calcineurin, which is essential for the activation of T-cells.
Additional formulations

**Novagali** – Cyclokat, a cyclosporine

**LuxBio** – LX214, a voclosporine
Antibodies

- **AIN457** (Novartis) – neutralizes IL-17A
- **ESBA105** (Alcon) – fragment against TNF-α
- **Belimumab** (GSK) – human monoclonal inhibits B cell activation factor
- **Rituximab** (Biogen) – murine/human anti-CD20 monoclonal
Inhibiting BAFF or BAFF + APRIL?

- Belimumab
  - HGS/Glaxo Smith Kline
  - Anti-soluble BLyS mAb

- BR3-Fc (BAFF-R-Ig)
  - Genentech/BiogenIdec
  - Soluble receptor that binds BLyS only

- Atacicept
  - ZymoGenetics/Merck-Serono
  - Soluble receptor that binds BLyS, APRIL and heterotimers

- Ligands
- Receptors
- BAFF-R
- BCMA
- TACI
- Proteoglycans

B-Cell
Other anti-inflammatory drugs

**CF-101 (CAN-FITE)** – oral adenosine3 receptor agonist, induces inflammatory cell apoptosis

**RGN259 (Regenerex)** – topical thymosin β4

**Perceiva (MacuSight)** – sirolimus, subconjunctival injection, inhibits response to IL-2
Resolvins
Goal – Break Cycle of Inflammation
SAR 1118 Binds to LFA-1 on T-cells and Prevents Interaction with ICAM-1

SAR 1118 Inhibits T-cell
1. LFA-1/ICAM-1
2. Adhesion
3. Migration
4. Proliferation
5. Cytokine Release

LFA-1: lymphocyte function-associated antigen-1 (CD11a/18; αβ2)
ICAM-1: intercellular adhesion molecule-1 (CD54)
TCR: T cell receptor
APC: antigen presenting cell
MHC II: major histocompatibility complex class II
Other anti-inflammatory compounds

- Rivoglitazone (Santen) – binds to PPARs
- Cilomilast (Alcon) – phosphodiesterase 4 inhibitor
- DA-6034 (Dong-A) – inhibits NF-κB activation
- Chitosan-N-acetylcysteine conjugate – thiolated polymer, suppresses inflammation, no effect on corneal staining
- Tranilast – inhibits lipid mediator and cytokine release
- N-acetyl aspartyl glutamic acid – neuropeptide
- Astaxanthin – oral carotenoid
- Curcumin - natural polyphenol extracted from turmeric
- Catechins – from green tea
- KLS-0611 & KCT-0809 (Kissei) - treat surface damage
Hydration

Oral sea buckthorn oil – reduces tear osmolarity

Lancutovide (Lantibio) – promotes hydration

Alpha eye dry eye relief mask – moisture barrier
Boundary Lubrication

Lubricin -

• Protects against shear stress
• Addresses central causative mechanism (i.e. shear stress) of ocular surface damage in dry eye disease
Virtual kaleidoscope of potential treatments for dry eye disease
Common signs and symptoms of dry eye disease do not correlate
Clinical Challenges in Dry Eye Therapeutics

- Existing treatments fail to address causative mechanisms
  - Inflammation is low gain, peripheral to central loop
- Difficult inclusion/exclusion criteria
  - Historically subjective signs
  - Symptoms & signs don’t correlate
- Schirmer strips and corneal staining are primary endpoints in most clinical trials, but their diagnostic value is limited
- Symptoms alone are insufficient to track severity
Schirmer Strip Severity Analysis

*Disease severity is calculated as an unbiased, normalized composite of seven clinical signs & symptoms.

\[ y = -38.375x + 24.905 \]

\[ R^2 = 0.1698 \]
Tear Film Breakup Time (TBUT) Severity Analysis

\[ y = -28.755x + 14.965 \]

\[ R^2 = 0.2987 \]
Corneal Staining Severity Analysis

\[ y = 18.442x - 3.0871 \]

\[ R^2 = 0.4339 \]
Symptoms (OSDI) Severity Analysis

\[ y = 126.91x - 14.381 \]
\[ R^2 = 0.4082 \]
Figure 2. Mechanisms of dry eye.
Hyperosmolarity is Bad

- Hyperosmolarity is recognized as the central pathogenetic mechanism of dry eye disease
- Hyperosmolarity is common across all forms of dry eye disease
- Hyperosmolarity causes epithelial cell death
- Hyperosmolarity causes inflammation
- Hyperosmolarity reduces the ability of mucins to lubricate
  - Loss of lubrication causes friction, which leads to wear
  - Wear roughens ocular surface
  - Rough ocular surface nucleates faster breakup times
Osmolarity Severity Analysis

\[ y = 128.17x + 280.2 \]

\[ R^2 = 0.5538 \]
Osmolarity is a Superior Marker of Therapeutic Efficacy

DataCourtesy Dr. BarisSonmez, Ondokuz Mayis Universitesi

Confidential 64
Osmolarity is a Superior Marker of Therapeutic Efficacy
We need new diagnostic approaches to help solve the puzzle of dry eye treatment.
Ocular Surface Disease Spiral

- Inflammatory Infiltrates
- Decreased Goblet Cell Density
- Irritation
- Decreased Tear Breakup Time
- Dehydrated Mucin
- Decreased Hydration
- Remodeled, Leaky Epithelium
- Increased Osmolarity

B Yerxa, 2003
Thank you for your attention