Overview & pathophysiology of Dry Eye and the use of cyclosporine eye drops in dry eye...

This Allergan® sponsored session was held on July 24, 2005, Hotel Satya Ashoka, Jabalpur. The session was followed by Dinner. Dr. Miss Paras Mehta was the invited guest faculty, Prof. Dr. R. K. Mishra was the moderator for the meeting.

Definition

o First described by Henrik S.C.Sjogren 1933
o Keratoconjunctivitis sicca
o Modern definition based on three layered concept (Holly and Lemp)

Dry eye is a disorder of the tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort.

Limitation of Definition

o Ocular surface damage is "INTERPALPEBRAL". Usually true but not always correct.
o "SYMPTOMS" of discomfort are known to be absent in some patients who have signs of dry eye.
o "DAMAGE to ocular surface" may not always be demonstrable with current methods.

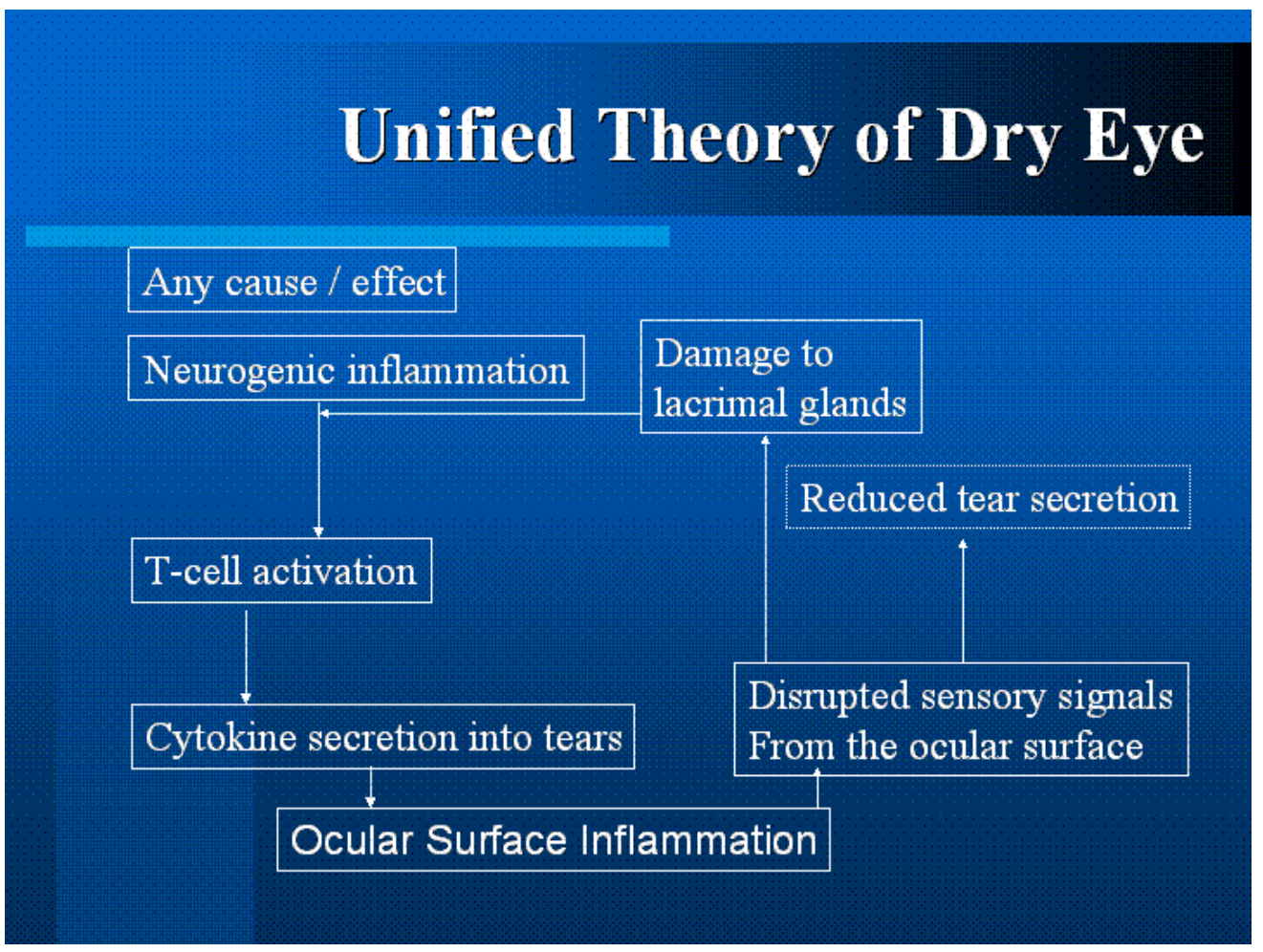
Global Criteria for Dry Eye

o Symptoms
o Interpalpebral surface damage
o Tear Instability
o Tear Hyperosmolarity

New knowledge

o Immunologic changes play a role in pathogenesis even in postinfectious and age-related condition.1
o More specific term: Ocular surface and Tear disorders.2

Unified Theory of Dry Eye



How important is all this?

o Is it relevant to the population?
o Is it relevant to the health policy?
o Should ophthalmologists care?

International prevalence

o Community studies: 15% in age group 55-72 years.1
o Cross-Sectional study: 5.5% to 10.8%.2
o Canadian Dry Eye Epidemiology Study (CANDEES): 28.7% reported symptoms, 7.6% moderate symptoms, 1.6% severe.Women 64:1.3

Present scenario

o Significant advance in understanding of pathogenic factors
o Lack of consensus on appropriate diagnostic criteria
o No Gold standards yet
o Prevalence of dry eye will increase as population above 60 years grows.
o Important and serious disease with significant impact on quality of life.

Present Indian Scenario

o No epidemiological data available
o Urban areas show significant increase in dry eye disease (anecdotal data)
o Understanding and diagnosis of dry eye disease still an major impediment in spread of treatment options
Single Significant Advance in Dry Eye Disease
o Understanding the role of (pro)inflammation in Dry eye disease
o Availability of anti-inflammatory options for long term treatment in patients with significant dry eye disease.

Dry Eye Disease: Prevalence

How Prevalent is Dry Eye?

o Dry eye is believed to be one of the most commonly diagnosed ocular conditions in the United States
- Most commonly observed among older women
o Few studies have accurately characterized the magnitude of the problem
- Evaluation of demographic characteristics may help define the population most at risk
o Schaumberg et al conducted a cross-sectional study to determine the prevalence of dry eye disease
- Women's Health Study population consisted of 39,876 female healthcare professionals
o Prevalence of dry eye increased with age
- 5.7% of women >50 years old vs 9.8% of women >75 years old
- Age adjusted prevalence of dry eye was 7.8% or
3.23 million US women
o Racial Differences
- Compared with whites, Hispanic and Asian women were more likely to report severe symptoms
o No difference in rate of clinical diagnoses
o Socioeconomic Factors
- No significant differences by income
- More educated women were less likely to have dry eye

Overall, Who is Most Likely to Have Dry Eye?

o Peri- and post-menopausal women
o 80% of dry eye patients are women
o Patients who wear contact lenses
o Patients with autoimmune disease
- Sjögren's syndrome

Which Patients Are Candidates for Therapy?

o There is no single method for determining if a patient is a candidate for dry eye therapy
o Criteria for starting therapy may include
- Patient symptoms
- Corneal and conjunctival staining
- Decreased TBUT
- Schirmer scores
o Patient symptoms and clinical signs should be considered when deciding on therapeutic intervention

Current Treatment for Dry Eye

o A majority of patients (74%) do not obtain satisfactory relief from dry eye symptoms with artificial tears
o Punctal plugs are not effective for all patients
o Many dry eye patients (34%) wish there was an effective therapy available for treating their dry eyes

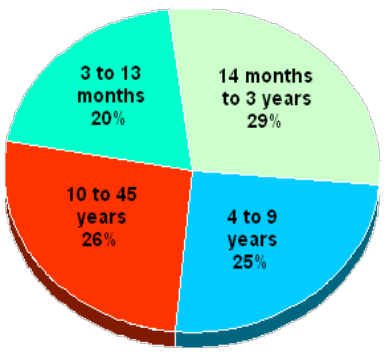
Conclusions

o Dry eye is a common ophthalmic condition that affects 3.2 million American women middle-aged and older
o Current treatment modalities are largely unsatisfactory

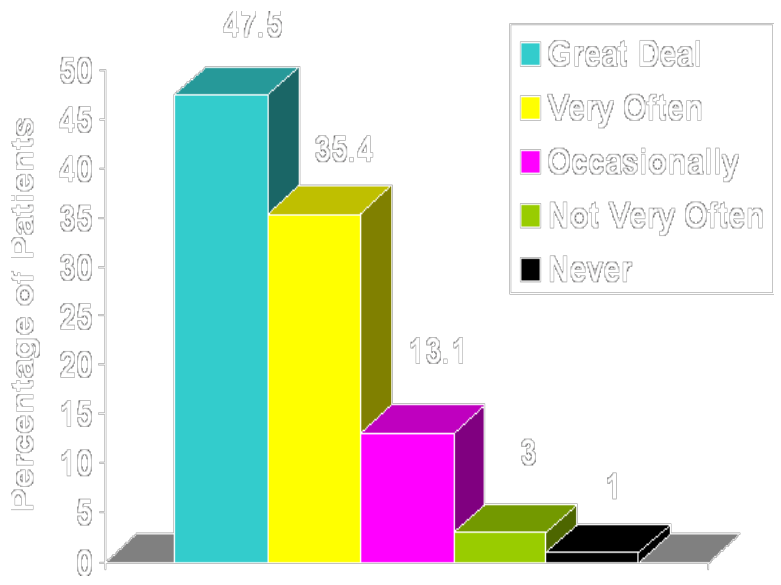
Patient Impact & Quality of Life - How Does Dry Eye Affect Patient QOL?

o In a recent survey of 100 patients with dry eye
- Patients reported that they suffered from dry eye for a median 48 months (mean 86.8 months, SD 103.9 months)
- Most patients (75.8%) felt that their dry eye had worsened over time

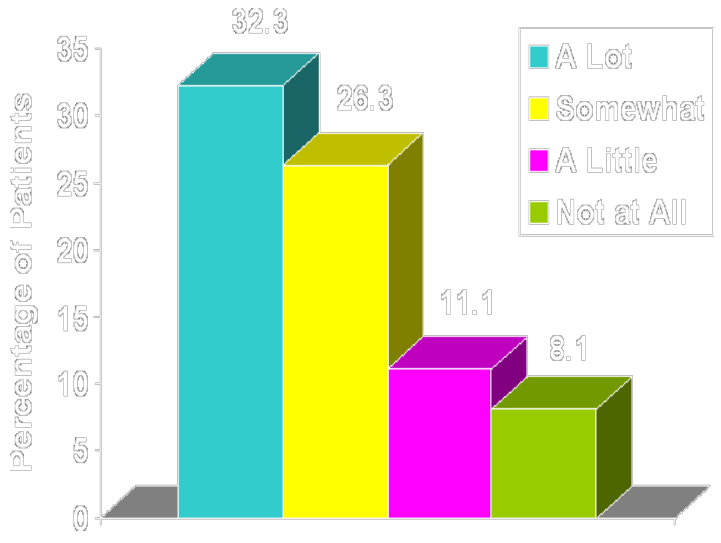
How Long Have You Suffered From Dry Eye

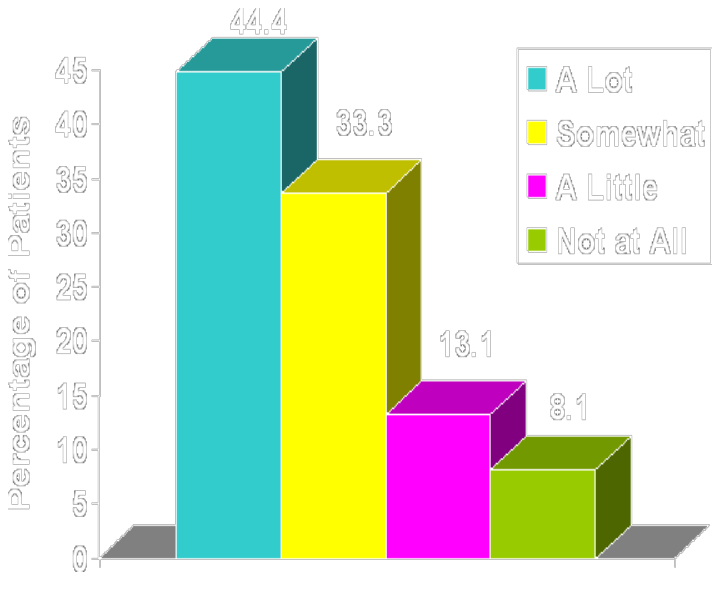


How Often Does Dry Eye Affect Your Normal Activities?

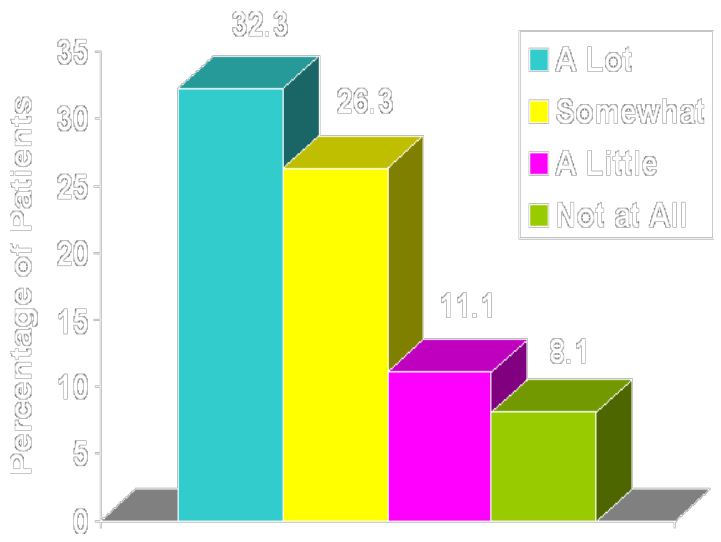


How Does Dry Eye Affect Your Reading?





How Does Dry Eye Affect Your Ability to Use a Computer?



Impact on Quality of Life

o Utility assessment of dry eye disease impact
- Time trade-off method
o Hypothetical question for patients
- How many years would you give up from the end of your life to be symptom-free now?
- Responses scaled from 0-1
o 0= death, 1= perfect health

Comparative Time Trade-off Scores

o The affect that moderate dry eye has on quality of life is comparable to that for moderate-severe angina

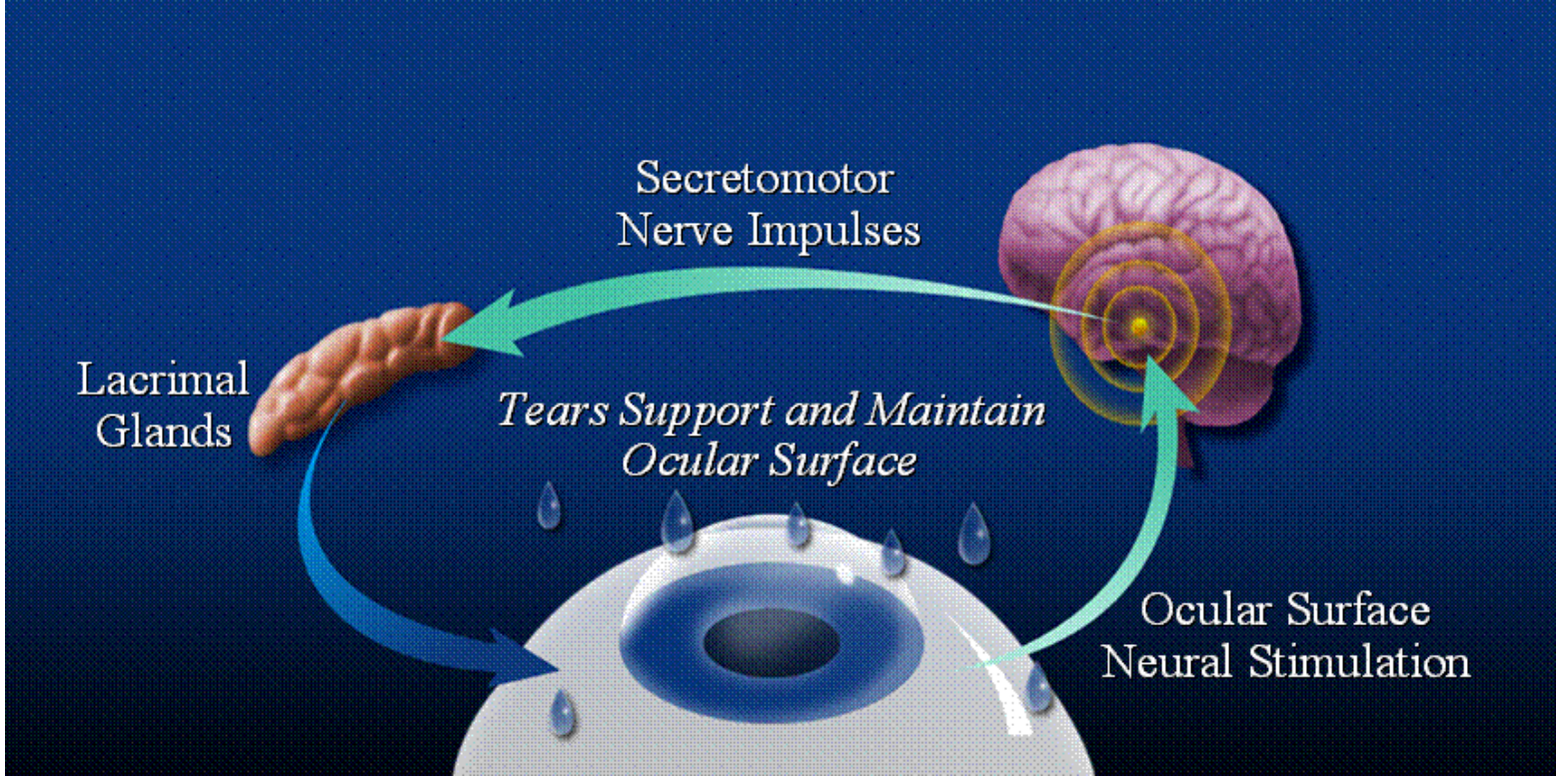
Summary:

Dry Eye Disease Affect on Patients
o Functional visual acuity significantly decreased
o The effect that dry disease has on quality of life is similar to that for moderate-severe angina

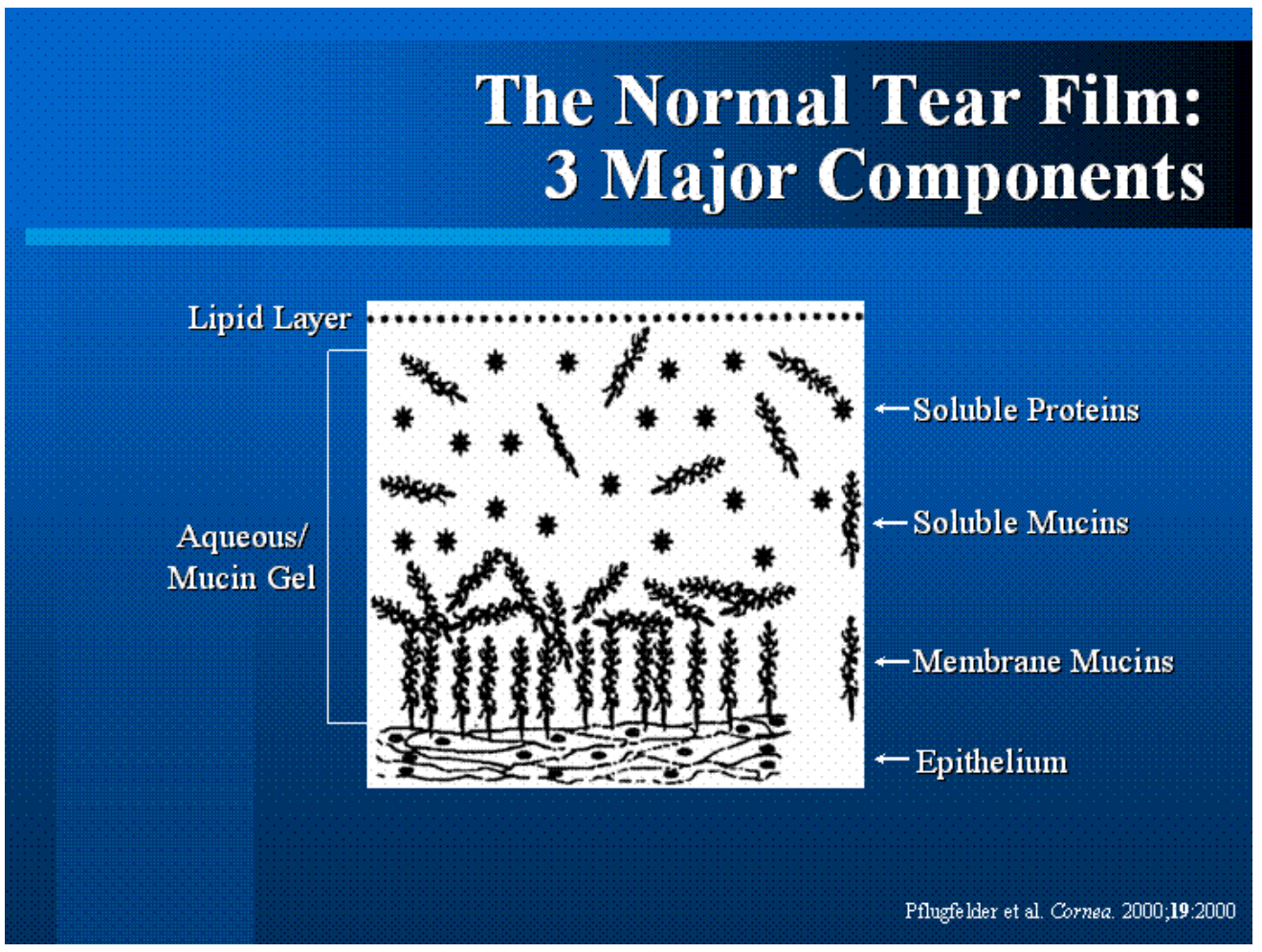
Conclusions
o Dry eye symptoms have an adverse effect on patients' lives
- It interferes with daily activities at home and at work
- It worsens over time
o Patients view their dry eye very seriously
o Utility for moderate dry eye (0.78) is similar to that for moderate angina

Pathophysiology

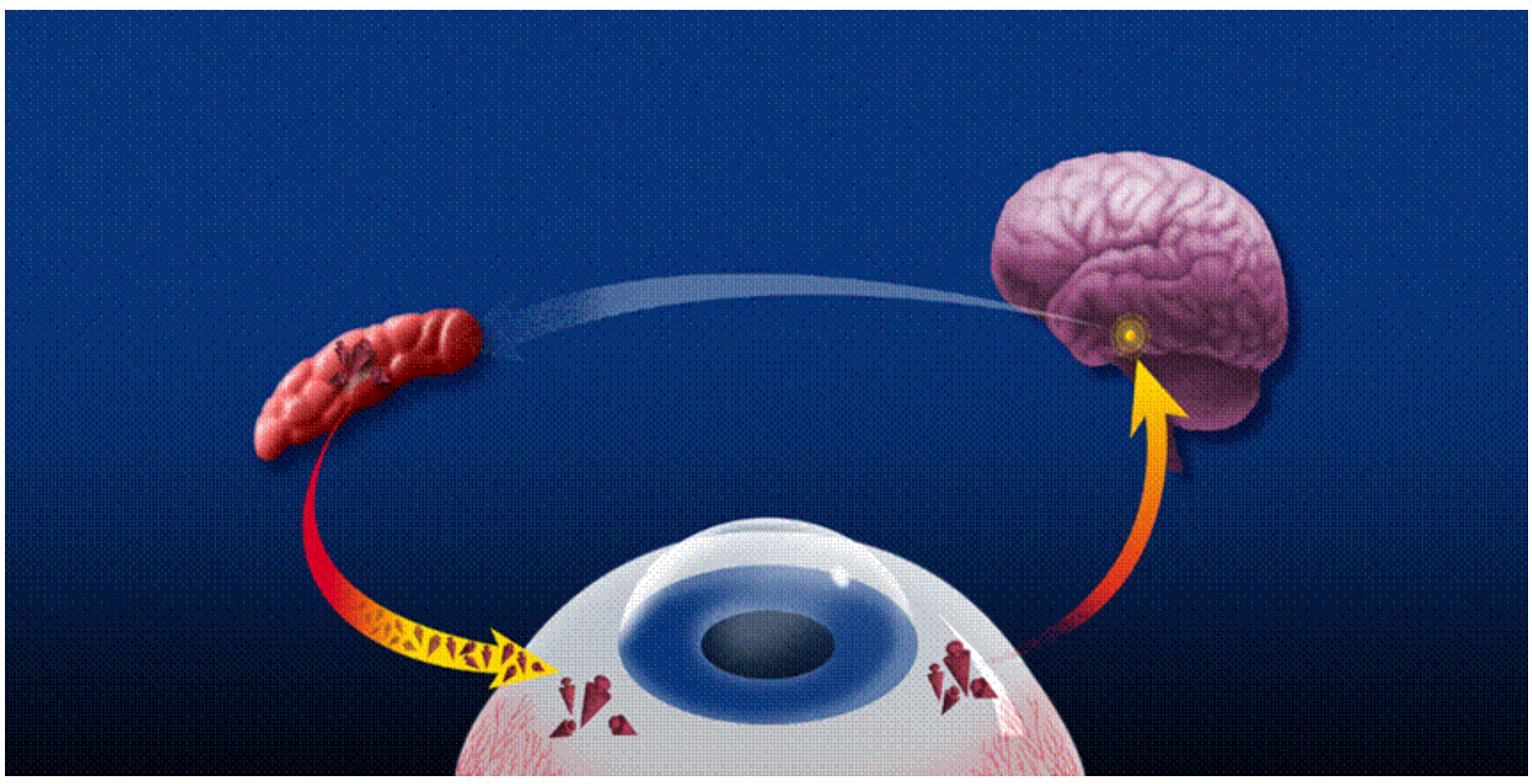
The Healthy Eye



The Normal Tear Film:
3 Major Components



Dry Eye Disease



Tear Quality and Quantity in Dry Eye Differs From Normal Tears

o Tear components in patients with dry eye differ in quantity and quality from normal tears (Ohashi et al, 2003)
- Lactoferrin levels are significantly lower in dry eye patients than in controls
- Epidermal growth factor is significantly decreased in dry eye patients
- These findings were consistent regardless of autoimmune status (Sjögren's and non-Sjögren's)

Conclusions

o Normal tearing depends on a neuronal feedback loop
o In dry eye, the normal neuronal control of tearing is disrupted
o Tear components in patients with dry eye differ in quality and quantity

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Cyclosporine Ophthalmic Emulsion 0.05%
What Is Restasis®?

o Ophthalmic cyclosporine 0.05% emulsion
- Contains the immunomodulator cyclosporine
o Cyclosporine inhibits T-cell activation thus restoring natural tear production
o Restasis® ophthalmic emulsion increases tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca . Increased tear production was not seen in patients who were currently using topical anti-inflammatory drugs or in patients who use punctal plugs
o Restasis® ophthalmic emulsion is contraindicated in patients with active ocular infection
- It has not been studied in patients with a history of herpes keratitis
o The most common adverse event was ocular burning (on instillation- 17%)

How Does Restasis® Work?
(Cyclosporine 0.05% Ophthalmic Emulsion)

o Restasis® is believed to inhibit T-cell activation
(Kunert et al, Arch Ophthalmol. 2000;118:1489)
- Activated T cells produce cytokines that may result in
o Recruitment of additional T cells (Stern et al, IOVS. 2002;43:2609)
o Increased cytokine production (Pflugfelder et al, Curr Eye Res. 1999;19:201)
o Neural signal to lacrimal gland that disrupts production of natural tears
- Leads to a decrease in quality and quantity of tears
o Tissue damage in lacrimal glands and ocular surface (Yeh et al, IOVS. 2003;44:124)

The Restasis® Vehicle

o Oil-based ophthalmic emulsion
- Unique emulsion technology provides effective drug delivery to ocular tissue
- Efficacious at low cyclosporine concentrations
o Designed to solubilize cyclosporine
- Ensures penetration into surface tissue at low cyclosporine concentrations

Cyclosporine Is Effectively Delivered to Target Tissue

o Cyclosporine 0.05% ophthalmic emulsion
- Instilled BID in rabbits
o Cyclosporine in surface tissues
- Cornea-1550 ng/g
- Conjunctiva-713 ng/g
- Lacrimal gland-12 ng/g
o Intraocular cyclosporine
- Aqueous humor-1.4 ng/mL
- Retina- 0.7 ng/g

No Cyclosporine Detected in Blood

o Restasis® was instilled BID for 12 months to dry eye disease patients
o No cyclosporine was detected in blood (0.1 ng/mL)
- In trough samples taken before morning dose
- In samples 1 to 12 hours after the morning dose
- Systemic exposure to cyclosporine is thousands of times lower than blood levels achieved with oral cyclosporine dosing

Restasis® FDA Approval

o Based on two US and two non-US studies
- Included 1,200 patients with moderate to severe dry eye disease
o Evidence demonstrated statistically significant increases in Schirmer wetting vs vehicle at 6 months
o Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or in patients with punctal plugs

Phase III US Study Design
Patient Demographics

o No statistically significant differences
- Age
o Range 22 to 90 Years
o Mean 59 Years
- Gender
o 83% Female, 17% Male
- Race
o 86% Caucasian, 3% Hispanic, 3% black, 3% Asian
- Disease status
o 69% autoimmune disease free

Clinical Variables

Primary

o Objective
- Corneal staining
- Schirmer with anesthesia
o Subjective
- Blurred vision
- Artificial tear reliance

Secondary

- Photophobia
- Sandy/gritty feeling
- Burning/stinging
- Itching
- Dryness
- Pain

Tertiary Laboratory Variables

Conjunctival Biopsies
o Goblet cell density
o Number of T cells
o Degree of immune activation

Key Inclusion and Exclusion Criteria

Inclusion

o Symptomatic dry eye disease despite conventional management
o Schirmer <5 mm/5 min
o Corneal and interpalpebral conjunctival staining
o OSDI score

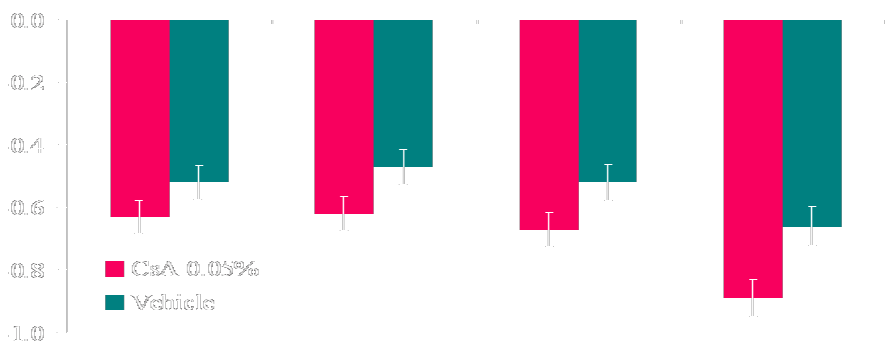
o Normal lid anatomy/blinking function
o BCVA Snellen 20/100

Exclusion

o Severe lacrimal dysfunction
- Nasal-stimulated Schirmer <3 mm
o Permanent goblet cell loss/scarring
o Active ocular infection
o Ocular rosacea
o Severe blepharitis/lid margin inflammation
o Punctal occlusion within 3 months
o Contact lens wear during study

Clinical Correlation

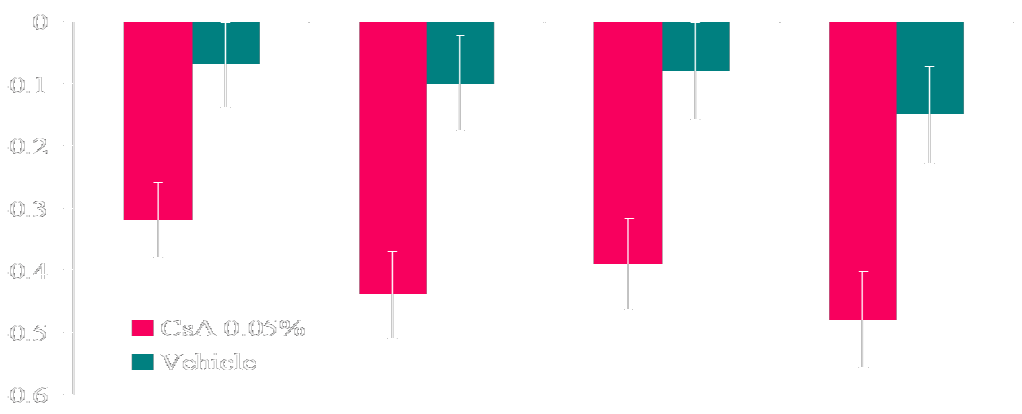
Improved Corneal Staining vs Vehicle



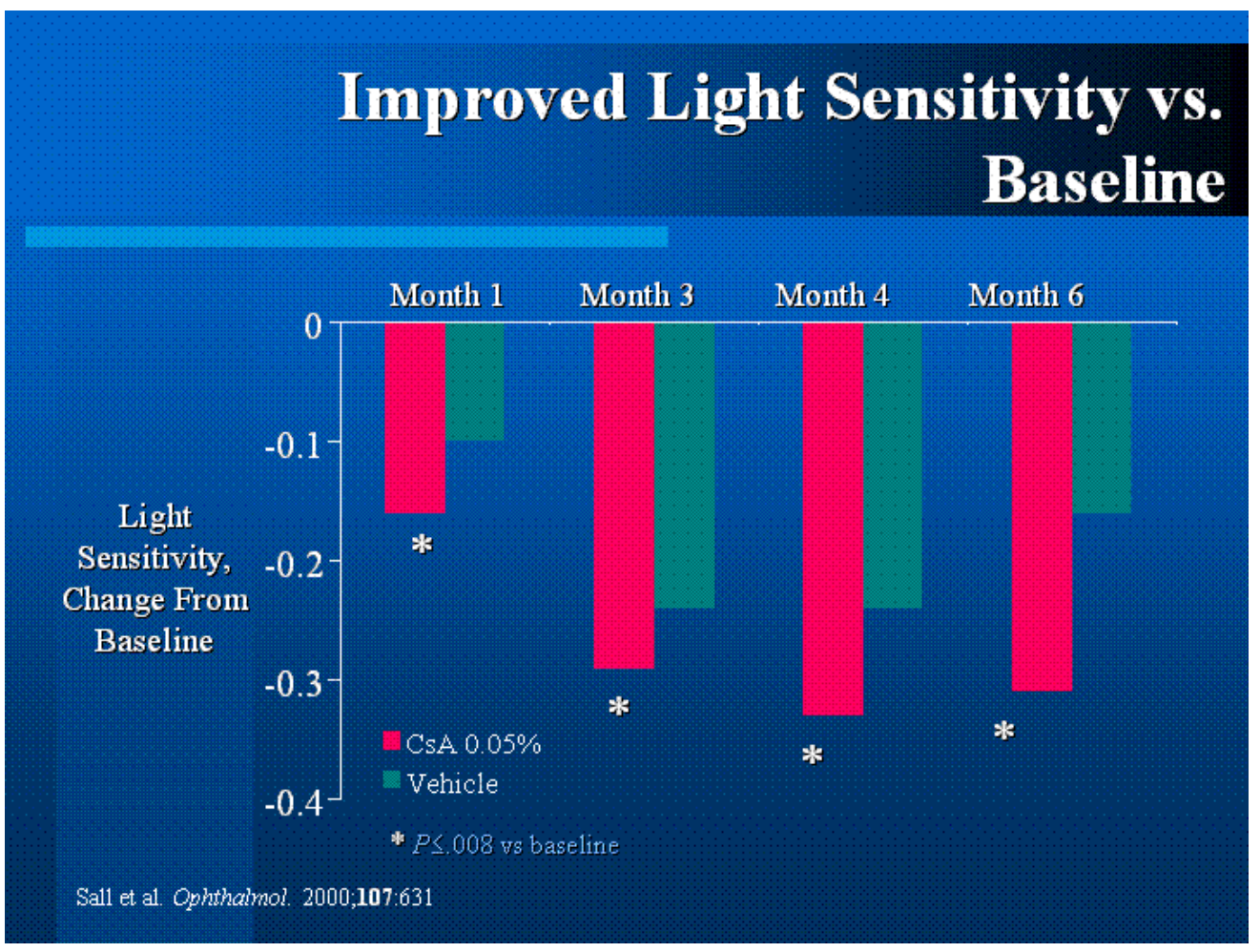
Restasis® Improves Schirmer Test Scores vs Vehicle

o A majority of Restasis® patients (59%) showed improvement from baseline Schirmer scores at 6 months (n=238)
- Significantly more Restasis® patients achieved >10mm improvement compared with vehicle
o Restasis®, 15%
o Vehicle, 5%
o Proven clinical correlation of symptom relief with increase in Schirmers
o Restasis® ophthalmic emulsion increases tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients who were currently using topical anti-inflammatory drugs or in patients who use punctal plugs

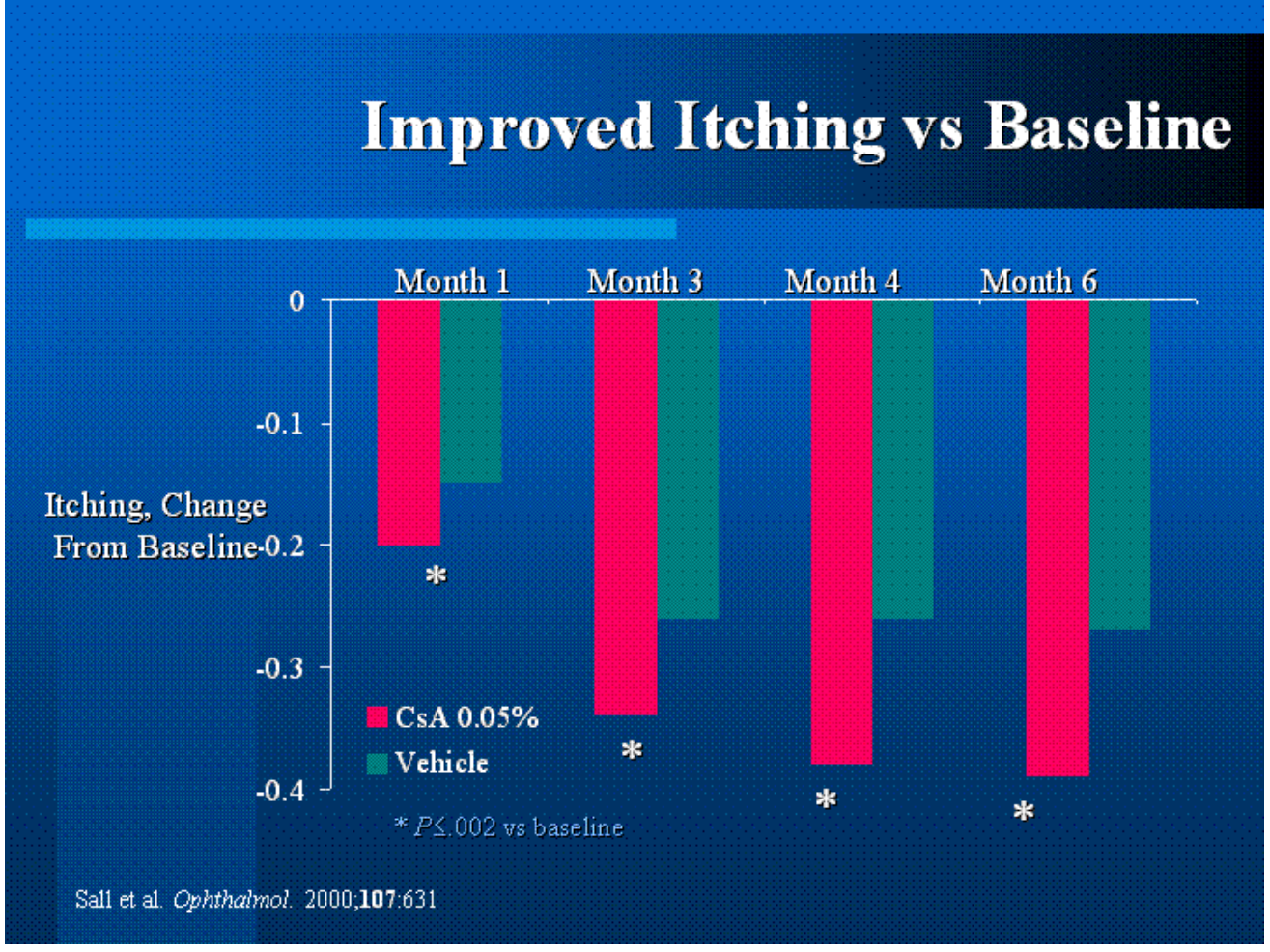
Improved Blurred Vision vs Vehicle



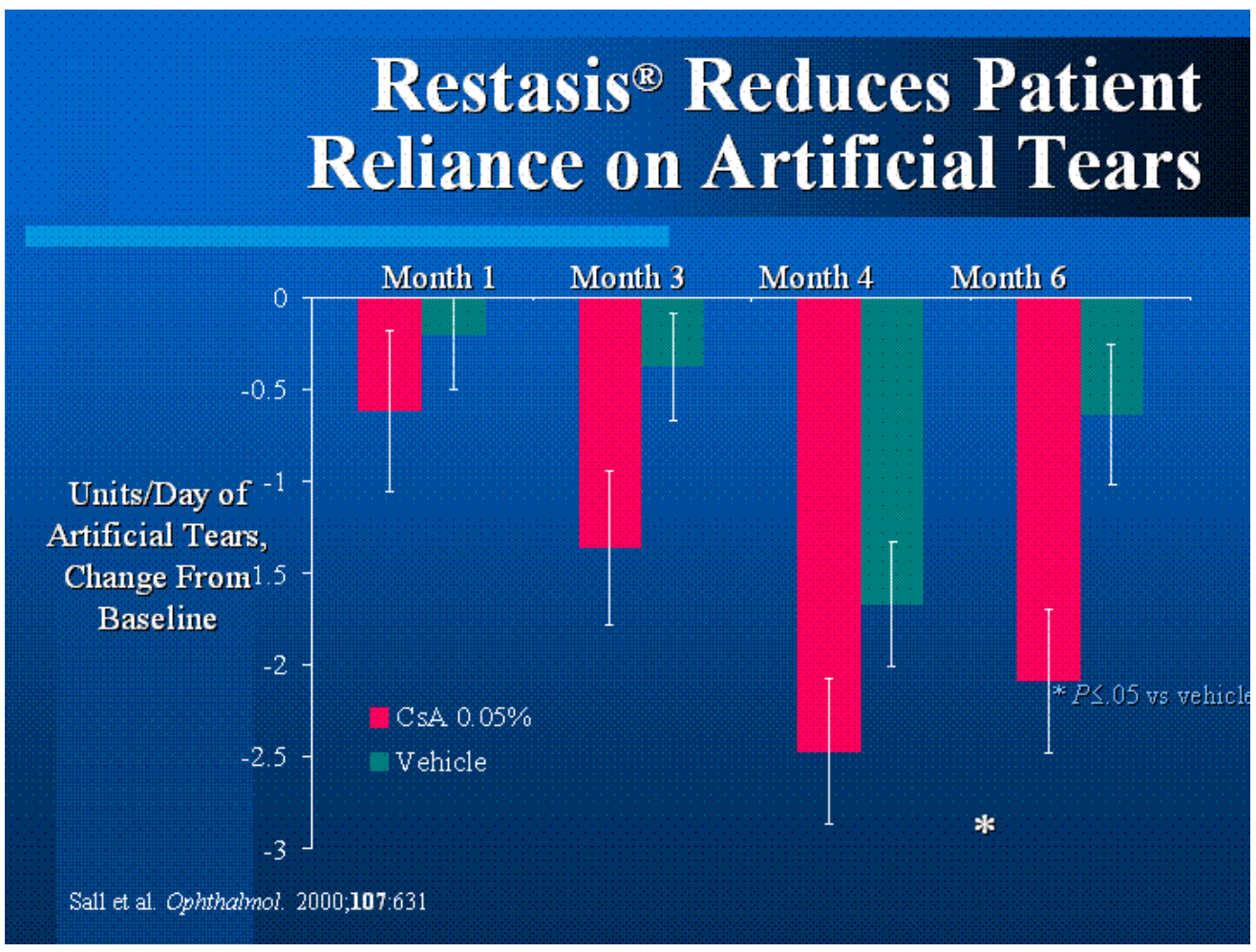
Improved Light Sensitivity vs. Baseline



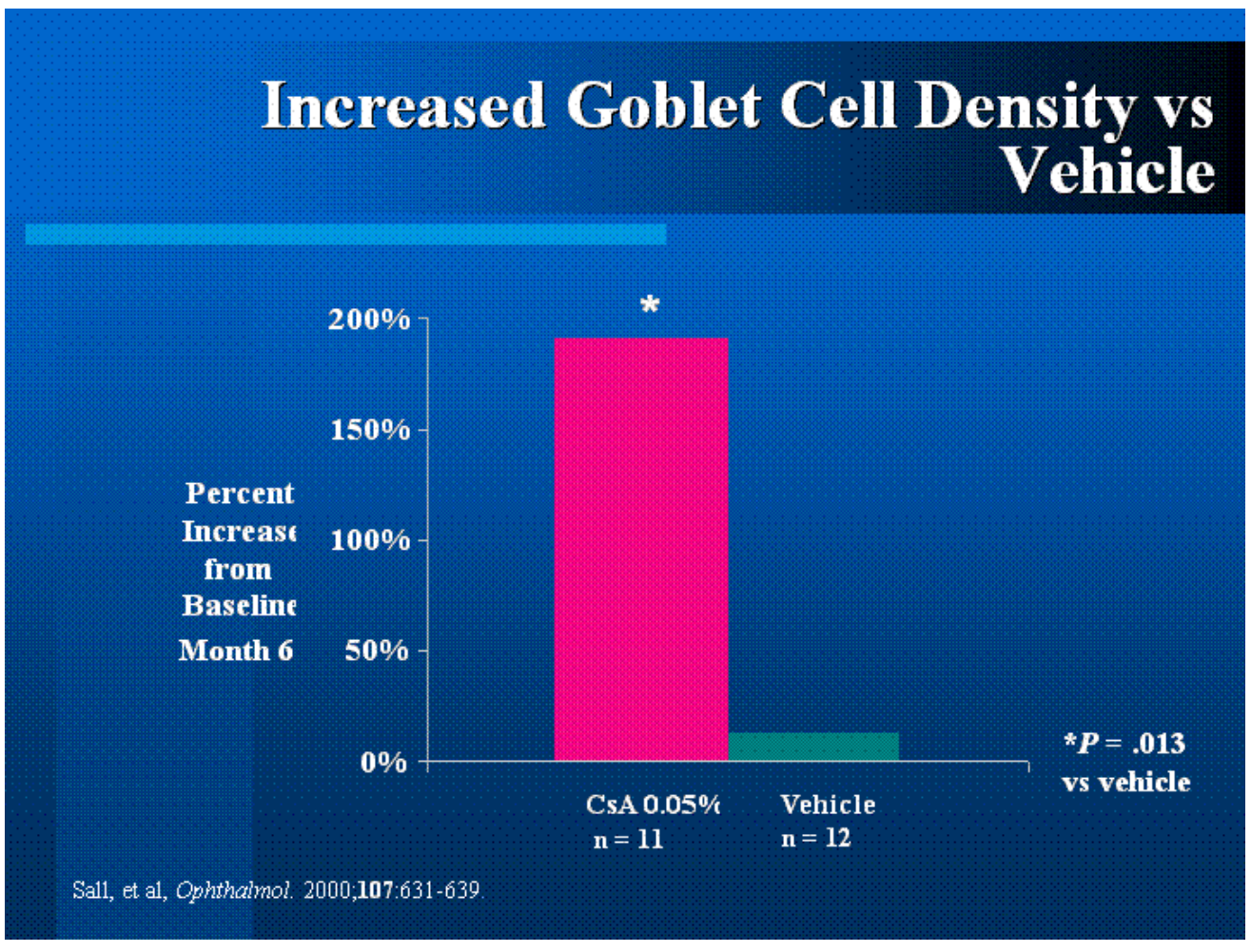
Improved Itching vs Baseline



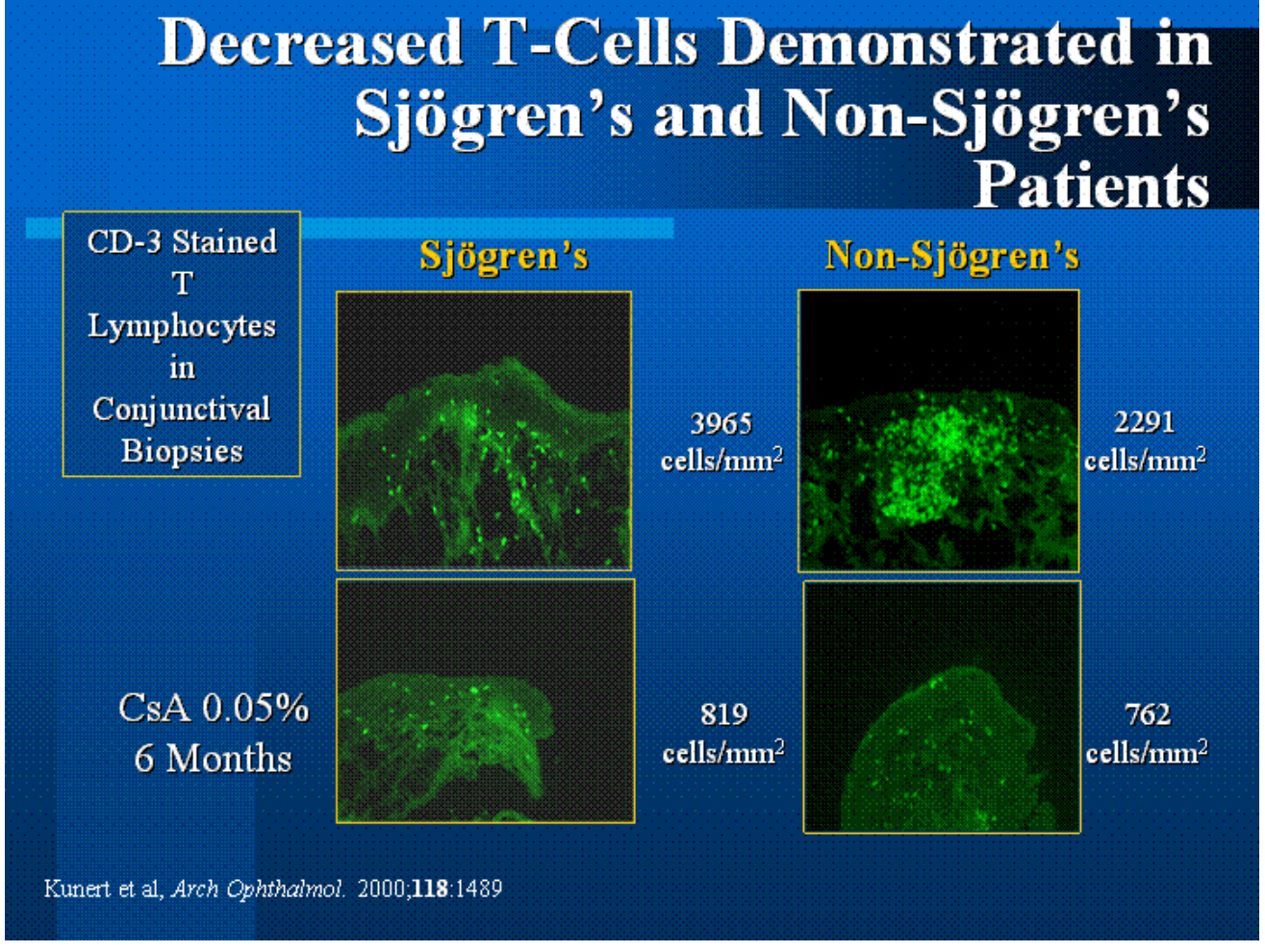
Restasis® Reduces Patient Reliance on Artificial Tears



Increased Goblet Cell Density vs Vehicle



Decreased T-Cells Demonstrated in Sjögren's and Non-Sjögren's Patients



Restasis® Reduces Indicators of Inflammation vs Vehicle

o HLA-DR and CD11a are markers of immune activation
- Reduced expression of these markers indicates resolution of inflammation
- After 6 months of 0.05% cyclosporine treatment, statistically significant decreases were observed for inflammatory markers HLA-DR and CD11a compared with increases in the vehicle group1
o Elevated inflammatory cytokines levels are found in tears and conjunctival tissue of dry eye disease patients
- After 6 months of treatment with 0.05% cyclosporine, IL-6 baseline levels were reduced significantly by more than 50%2

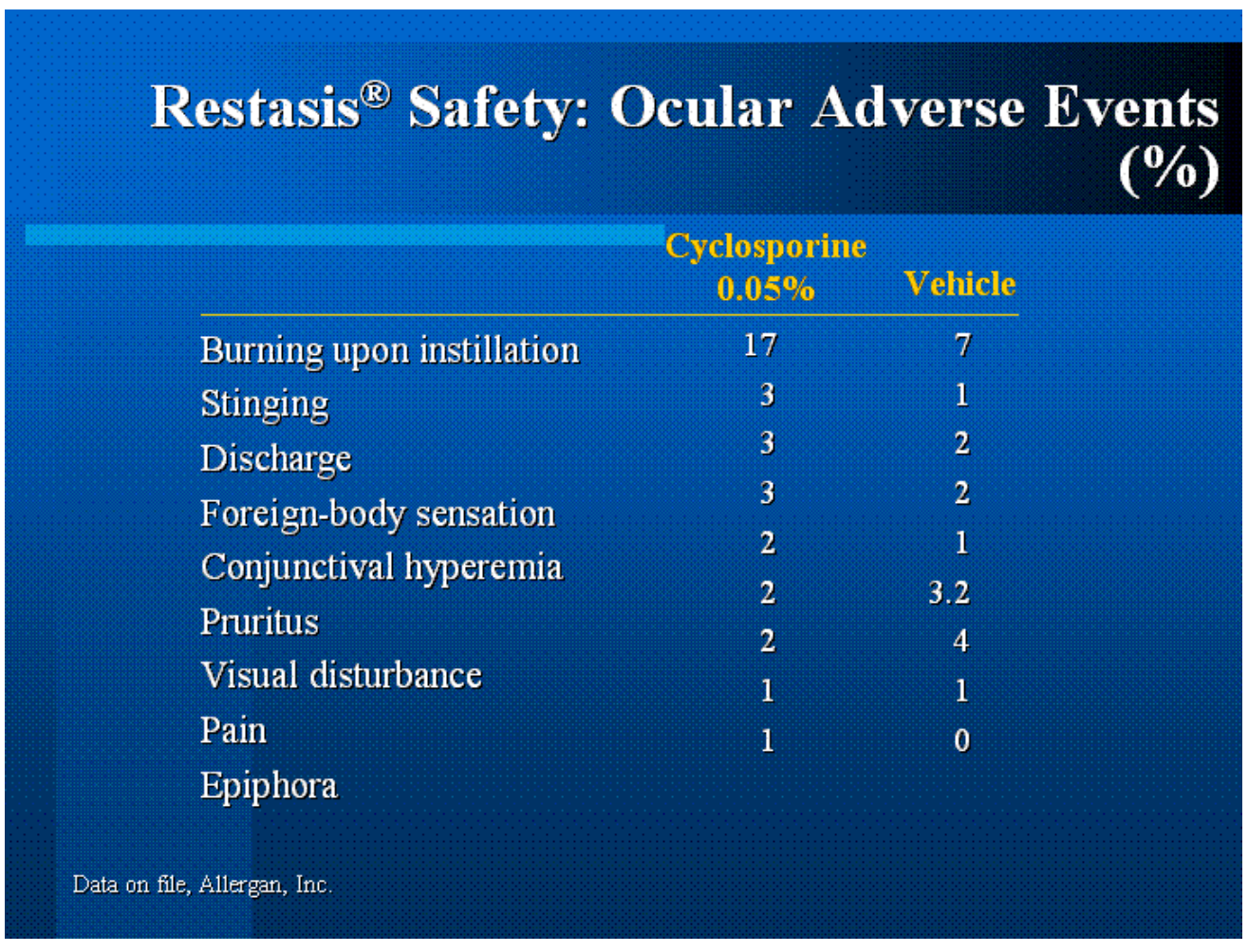
Conclusions

o Cyclosporine 0.05% treatment was superior to vehicle
o At month 6, increased natural tear production resulted in statistically significant improvements in Schirmer wetting scores
o Clinical correlation with improvement in
- Patient symptoms
o Dryness, itching, blurred vision, photophobia
- Corneal staining
o Cyclosporine reduces indicators of inflammation

Safety Assessments

o Adverse events
o Blood chemistry
o IOP
o Visual acuity
o Biomicroscopy
o Conjunctival microbiology
o Cyclosporine blood levels
Restasis® Contraindications
o Cyclosporine 0.05% ophthalmic emulsion (Restasis®) should not be used in patients with
- Active ocular infection
- Previously demonstrated hypersensitivity to the active molecule or any of the ingredients in the formulation

Restasis® Safety: Ocular Adverse Events (%)



Other Safety Results

o No increase in ocular infections
o No differences in blood chemistry, hematology
- Including renal and hepatic function
o No treatment-related changes in IOP, visual acuity,
or biomicroscopy
Systemic Safety
o No detectable cyclosporine in blood of any Restasis®-treated patient (0.1 ng/mL)
o Toxicity associated with systemic cyclosporine was not observed with cyclosporine 0.05% emulsion

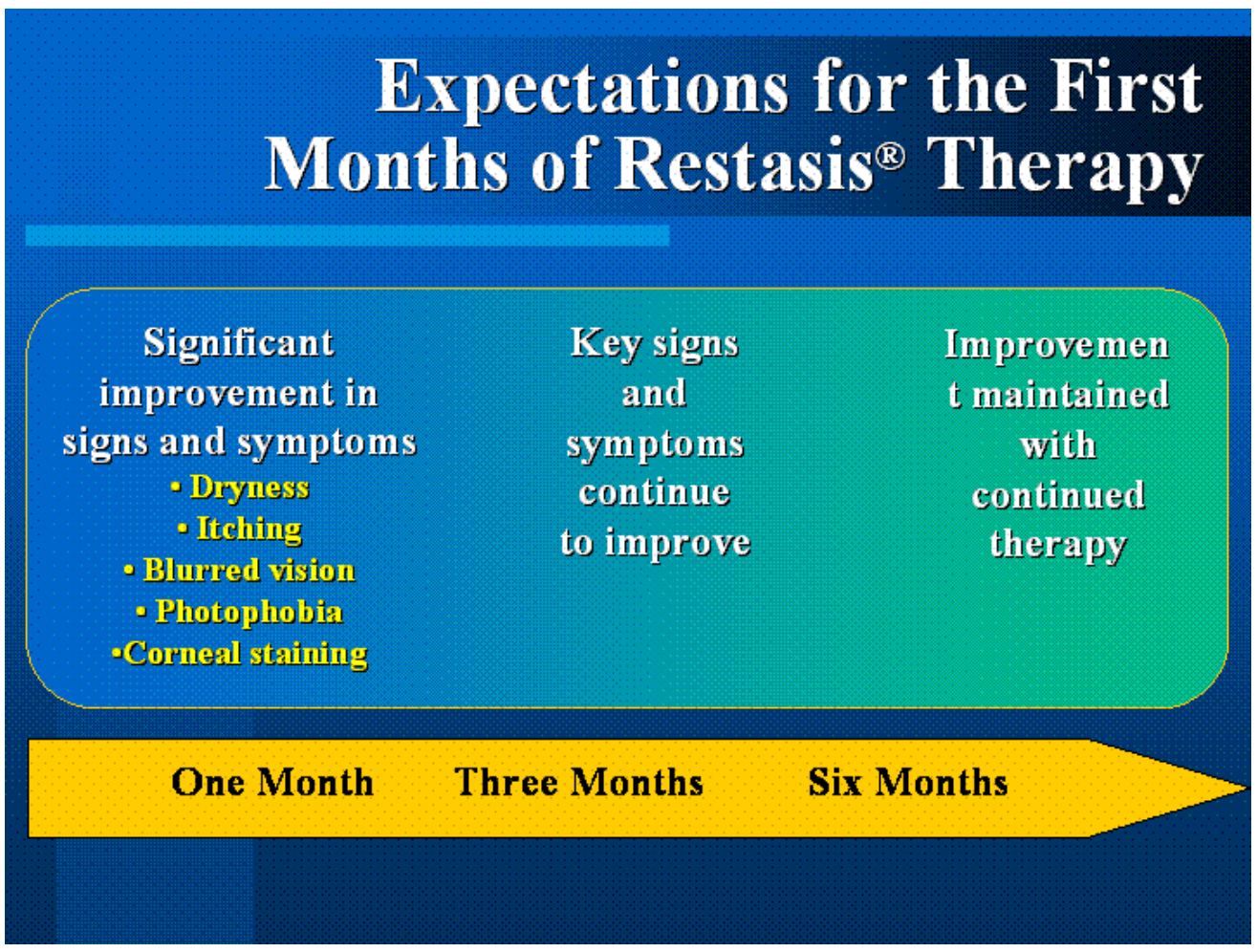
Restasis® Candidate Profile

o Restasis® increases tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or in patients using punctal plugs

Restasis® Dosing: BID

o Recommended Restasis® regimen
- 1 drop in each eye every 12 hours
- Inform patients: do not use "as needed" like traditional drops
o Concomitant aqueous tears
- Nonpreserved tears were used in clinical trials
- Allow 15-minute interval between instillations
- Additional emulsion may be poorly tolerated
o Contact Lenses
- Remove contact lenses before administering Restasis
- Wait 15 minutes before replacing lenses

Expectations for the First Months of Restasis® Therapy



Do Patients Need to Use Artificial Tears with Restasis®?

o For additional comfort and relief of dry eye symptoms, some patients may still need to use artificial tears
- Need for concomitant use should decrease over time
o Refresh® Liquigel®, Tears®, and Celluvisc® Lubricant Eye Drops are known to effectively improve patient comfort and offer relief of dry eye symptoms
- Refresh® brand were the only artificial tears used in the Restasis® Phase III clinical trials
o Refresh® Brand provides comfort and safety
- Effectively lubricates eyes
- Comfortable for sensitive eyes
- Composition resembles natural tears
- Safe to the ocular surface

Summary: Restasis® (Cyclosporine Ophthalmic Emulsion 0.05%)

o First and only therapy that restores natural tear production by treating the underlying cause of dry eye disease
o Safe and effective
o BID dosing
o Excellent results with adherence to therapeutic regimen
Note: The most common adverse event reported following Restasis® use was ocular burning (17%). Other ocular adverse events reported by 1% to 5% of cyclosporine patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign-body sensation, stinging, and visual disturbance

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