

Therapeutic Optometry Practice of the Future

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Optometry's role and future trends

Gatekeeper roles taken to the highest level

- Medical optometry
- The projections for cataract surgical volume
- Optometry's greatest opportunity
- Growth in optical and CL
- The place for all ocular health needs

The Trend is your Friend

- Diabetes
- Retina and injection medications
- Preventive medicine
- Cataract surgical volume
- Aging population diseases of the baby boomer generation
- Role in cost containment of chronic diseases

Intraocular Surgery and Optometry's Role

- Crystalline Lens Extraction
 - Toric IOLS
 - STAAR Surgical
 - Alcon
 - Multifocal IOLs
 - AMO-ReZoom
 - Alcon-ReStor
 - B&L-Akreos
 - Accommodative IOLs
 - Eyeonics/B&L-Crystalens
 - Tetraflex
 - Clear lens extraction
 - Early presbyopia
 - Hyperopia in pre-presbyopic ages
- Bi-manual phakoemulsification

Phakic IOLs-Moving refractive surgery away from the surface

- General advantages and disadvantages of intraocular applications

Optical

Physiological

Complications

Anterior chamber phakic IOLs

Verisyse (Artisan)-iris fixated lens-FDA approval

Excellent optics-high myopia and hyperopia corrections

Good contrast sensitivity

Large incision (6.5mm) PMMA lens

Progressive endothelial cell loss in some patients

Many implanted internationally

Complications and post-operative management

Posterior Chamber Phakic IOLs

Visian Implantable Collamer Lens (ICL)

Collamer hydrophilic material-non coating collagen component

Ciliary sulcus positioning for fit/centration

High myopia, low hyperopia and astigmatism corrections

Many implanted internationally

Complications may be cataracts, pigment dispersion and glaucoma in isolated cases

FDA Ophthalmic Device Panel approval

Anterior Segment OCT Applications:

Refractive Surgery and Anterior Segment

Refractive Surgery

Corneal laser refractive surgery

Phakic IOLs

Corneal refractive implants

Anterior Segment Imaging and Surgery

Corneal Imaging and Measurement

Iris Imaging and Evaluation

Trauma Assessment

Crystalline Lens Imaging and Evaluation

Keratoplasty Techniques:

Lamellar Surgery

Limbal Stem Cell Deficiency

Sequelae

- Persistent epithelial defects
- Corneal scarring and ulceration
- Conjunctivalization of the cornea
- Severe visual loss
- Chronic pain
- Keratoplasty failure
- Keratolimbal Allograft

Dry Eye and Ocular Surface Disease

Androgen-Hormonal Theories

- Mather WD Cornea July 1998 “Menopause and tear function: the influence of prolactin and sex hormones on human tear production”
- Common for dry eye onset to be perimenopausal
- Looked at estrogen and prolactin levels on tear function (N=110)
- Serum levels measured for hormones
- Osmolarity, tear volume, Schirmer’s, tear flow
- Hormone replacement was a negative correlation to dry eye
- Total testosterone was a positive correlation to dry eye
- Krenzer KL et al. J of Clin Endocrinology Metab “Effect of androgen deficiency on the human meibomian gland and ocular surface”
- Patients with androgen deficiency (anti-androgen therapy) had:
 - Significant increase in tear film debris, abnormal tear meniscus, conj injection etc.
 - Significant increase in vital dye staining
 - Significant decrease in TBUT and meibomian gland secretion quality
 - Significant increase in symptoms (discomfort, photophobia and blurred VA)
- Sullivan DA et al. AM NY Acad Sci Jun 2002 “Androgen deficiency, MGD and evaporative dry eye”
- Conclusion:
- The meibomian gland is the androgen target organ and may promote meibomian gland dysfunction and evaporative dry eye
- Concurrence with Cermak JM et al Cornea 2003 Aug
- Auw-Haedrich Grafes Arch Clin Exp Ophthalmol. Sept 2003
- “Estrogen receptor expression in meibomian glands and its correlation with age and dry eye parameters”
- No correlation between estrogen receptor positivity and dry eye symptoms

Therapies

- 3% Testosterone suspended in a topical cream
- Androgen tears
 - Phase II completed in mid-2005
 - Focus on meibomian gland function and lipid layer
 - Early results not reported

Cyclosporin Applications

- Novagali Pharmaceuticals
- Cleared Phase II and beginning phase III
- Nova22007 is drug name at this point
- Indication for dry eye

- LX201 by Lux Biosciences
 - Sustain release drug implant to prevent rejection post transplant and graft failure
 - 1/3 of graft failures are attributable to rejection
 - Monitor at 4-6 week intervals for 1 year

Tetracyclines in MGD

- 54% had improved symptoms and OSD (marginal infiltrates, PEE, redness) after 6 weeks of oral oxytetracycline (Bartholomew et al. BJO 1982)
- 96% had ↓ irritation symptoms and ↓ redness after 6 weeks of oral doxycycline therapy (Frucht-Perry et al. AJO 1993)
- 98% had ↓ irritation symptoms, ↓ redness and arrest of conjunctival scarring on oral TCNs (Akpek et al. Ophthalmology 1997)
- Antibiotics inhibit bacterial protein synthesis by binding 30S ribosome
- Anti-inflammatory properties
 - decreases IL-1, TNF-
 - decreases NO production
 - decreases HLA Class II antigen expression
 - decreases metalloproteinase production and activation
- Decrease symptoms and joint destruction in RA

Smith VA, Cook SD Br J Ophthalmol May 2004

- Doxycycline irreversibly inhibits corneal MMP activity by chelating the metal ions that are catalytically essential

Darsun D et al. Am J Ophthalmol July 2001

- Treatment of recalcitrant recurrent corneal erosion with inhibitors of MMP-9:
- Inflammation as root cause
- Doxycycline and corticosteroids

Doxycycline 50 mg or 20 mg bid

- Less phototoxicity than tetracycline 250mg
- Less gastritis
 - BID not before bed
 - No acidic beverages
 - With food (provided no dairy)

ALODOX Kit

Doxycycline Applications

- Chronic Blepharitis
- Meibomian Gland Disease
- Acne Rosacea
- Infectious keratitis

Topical Tetracycline or other anti-inflammatory medications

- Topical doxycycline – Alacritty biosciences
- Topical calcineurin inhibitors

Tacrolimus, Pimecromilus (Elidel)

- Ocular versions in the pipeline for ocular surface disease

Future Therapy

Diquafosol tetrasodium (Prolacria)

- Nichols KK, Yerxa B, Kellerman DJ
- Invest Drugs. 2004;13(1):47-54
- P2Y2 receptor agonist

Leads to rehydration through the fluid pump mechanism of accessory lacrimal glands (mucin & some lipid)

- Murakiami T et al. Ophthalmic Res Mar 2004
- Diquafosol elicits increases in net CL- transport through P2Y2 receptor stimulation in rabbit conjunctiva
- Causes secretion from the serosal to the mucosal side via stimulation of the P2Y2 receptors in rabbit corneas
- Tauber J et al Cornea Nov 2004
- Double-masked, placebo-controlled safety and efficacy trial of diquafosol tetrasodium ophthalmic solution for the treatment of dry eye
- Significantly lower staining scores compared to placebo at 6-week ($P < 0.001$) and continued throughout the 24 week period
- Schirmers ($P < 0.030$)
- Improvement in symptoms (primary end point – FB sensation)
- Shown to stimulate both aqueous and mucous secretion in humans – Li DQ et al.
- Beneficial results on corneal epithelial barrier function – Fujihara T. et al.
- Shown to stimulate mucin release in rabbit goblet cells – Fujihara T et al.

Rebamipide (Otsuka pharm)

Urashima H et al Cornea August 2002

“Rebamipide increases the amount of mucin-like substances on the conjunctiva and cornea in the N-acetylcysteine-treated in vivo model”

Also has hydroxyl radical scavenging effects on UVB-induced corneal damage in mice

- N-cetylcyteine to remove all filaments (mucin strands) to begin at base 0
- Then measured the amount of mucin-like substances on the conjunctiva and cornea (Alcian-blue)
- Rebamipide increased mucin and improved vital dye staining
- ARVO 2005 (Donshik et al)
- 200 patients over 12 weeks

- Primary end points
- Corneal fluorescein staining

- Secondary

Lissamine green & schirmers

- Favorable trend at 12 weeks in FCS, Lissamine and primary symptoms
- Statistical for Schirmers

iDESTRIN (NP50301)

- Nascent Pharmaceuticals
- 90 Patient 14-week Phase IIb
- For the treatment of dry eye in postmenopausal women
- Met primary end point on Schirmer's scores
- Improvement of > 75%
- Met secondary endpoint of SPK/corneal staining
- Unknown MOA

Ecabet Sodium

- Ista pharmaceuticals bought from Senju Pharmaceuticals
- QID for 90 days
- 112 patients in phase IIb
- Strong trend results for blink rate and in the OSDI
- Positive trend result in most bothersome symptom improvement
- A single instillation elicited a statistically significant increase in tear mucin in dry eye patients – *Madsuda K et al. ARVO 2003*

Gefarnate - Santen

- Promoted mucin production after conjunctival injury in monkeys – *Toshida H et al – Cornea 2002*
- Also shown to stimulate mucin-like glycoprotein from rat cultured corneal epithelium as well as in vivo rabbit eyes – *Nakamura et al.*

Diagnostic Advances

- OcuSense TearLab
- Europe C Mark approval March 2007
- Expected to reach US mid 2009
- 10 milli-microliters of tears

Oasis Medical

- Developing hand-held tear osmolarity instrument
- Expected late 2009 or early 2010

Osmolarity instruments:

- Instant measurements of osmolarity in your clinic!
- Initial patient pay model
- Eventual application for coding and billing specific to diagnostics
- IgE and other markers to follow

Future Therapy: Uveitis

- Calcineurin inhibitors

Pimecromilus, Tacrolimus

-for posterior and anterior uveitis

- LX211 clinical trials begin in 2007
- Infliximab (Remicade, Centocor Pharmaceuticals)

-Behcet's disease

-May facilitate early resolution of severe ocular disease but without long-term side effects

-Biologic anti-inflammatory drugs

-Target specific cytokines or other mediators

- In Behcet's disease the cytokine TNF- α seems to be the key mediator
- Embrel, infliximab and adalimumab are all TNF- α inhibitors (also used for cancer treatment)
- Rituximab appear to target IL-2 (which may target JRA Uveitis)
- Downside:

Serious side effects including infectious, TB, allergic disease, and flu-like reactions, shortness of breath, skin lesions and thrombosis (Arch Ophthalmol. 2005; 123:903-912)

IV medications currently

\$2400 per infusion and requires 6-8 per year

Posurdex

- Targeting Diabetic CME
- All chronic CME options
- Phase III clinical trials!

Drug Delivery Systems

- Retisert
- Fluocinolone acetonide implant about the size of a grain of rice
- Lasts for 30 months (2.5 years)
- Changing peoples lives
- JRA, Posterior uveitis, CME

MUTT (Multicenter Uveitis Treatment Trial)

- Began in 2007
- Sponsored by NEI
- Comparison of IV fluocinolone acetonide implant to systemic corticosteroid/immunosuppressive therapy (including biologic agents)

Anti-viral Therapy

- Topical N-chlorotaurine
- Pre-clinical trials promising using in vitro rabbit eyes
- Adenovirus serotypes for viral conjunctivitis
- N-chlorotaurine showed concentration dependent direct inactivation of all tested virus serotypes

- Fewer positive cultures and shorter duration of virus shedding
- Currently in phase I in Europe

Allergic Eye Disease Therapy

- Atopic keratoconjunctivitis
Tacrolimus ung applied to lids
- Bepotastine
H-1 receptor antagonist
ISTA pharmaceuticals
- Off label medications
Elidel (Pimecromilus 1%) topical to lids

Drug Delivery Systems

- Atopic keratoconjunctivitis
- New Drug Delivery Systems
- DuraSite
- Contact lenses with Allergy meds
- Punctal plugs

Anti-bacterial Testing: Genomics

- Microfluid Chip
Performs DNA sequencing
Rapidly identifies bacteria
Instantaneous - < 1 second
Compared to lab plating techniques that average 14 – 48 hours

Allergic Eye Disease

- Bepotastine besilate – Ista Pharm.
- North American rights from Senju Pharm.
- Non-sedating, selective H1 antagonist/mast cell stabilizer and eosinophil migration suppressor
- Currently in Phase III clinical trials
- Was an oral pill in Japan, this will be an eye drop in North America

Allergic Eye Disease

- Bilastine – Inspire Pharmaceuticals
- Oral antihistamine – H1 selective
- Completed phase III in Europe for allergic rhinitis
- Begin with oral formulation in N. America
- Will likely develop an ocular formulation soon after

Vekacia for VKC

- Novageli pharmaceuticals
- FDA orphan drug designation
- Is a cationic emulsion
- US Phase II trial was announced in April 2007
- Both symptoms and signs of the disease improved in children tested
- Safe and well tolerated

Technologies of the Future

- Statins for Cataract or AMD
- Australia's Center for Vision Research suggests that Statins may have protective effects
- Blue Mountain Eye Study – re-examined 2335 participants at 5 years and 1952 at 10 years
- Although it did not find statins to be associated with early AMD incidence it was protective for soft drusen (precursor to AMD)
- Reduced the risk of cataracts – all types

Transscleral Drug-delivery device

- NEI funded
- Posterior segment diseases
- Involves micro-needles and nanoparticles
- Alternative to injecting directly into the vitreous
- Chronic CME, CMV, posterior uveitis etc.

Nanotechnology

- Defined as devices or systems with a length scale of 1- 100 nm
- Currently 8% of nanotechnology is in medicine
- Tissue engineering
- Drug delivery systems (nanocarriers of drug)
- Nanomolecule with anti-infective properties

VivaGel – Starpharma

- A microbicide that works by inhibiting HSV-2 and HIV
- Very effective in clinical trials in Australia
- A short jump to HSV-1 (ocular)
- Wound sealing after a traumatic injury
e.g. corneal or conj lacerations
- Can prevent scarring at nano-technology level
- Create scaffolding nanostructures which allow nerves regeneration
- Called self-assembling peptide nanofiber scaffolds
- Will assist with nerve regeneration such as optic nerve regeneration and even spinal cord injuries
- Still need to assess safety in humans.

Other Nanotechnology

- Lab on a chip will replace culturing
- Take specimen from tear film or cornea
- Place it on microchip
- Digital read-out in minutes to identify the microbial pathogen

Transscleral Drug-delivery device

Injectable medications

- Avastin
- Anti-VEGF

- Now preventive for Diabetes
- Vitreous floater treatments

Diabetes and Diabetic Retinopathy

- Prevalence of Diabetic Retinopathy In Adults With Diabetes Mellitus
- Prevalence of Diabetic Retinopathy Type 1 vs. Type 2

Vitreosolve® - A Note On Safety

Current Clinical Trial: Study Rationale

- VRT's Phase I and II data demonstrates excellent safety profile of Vitreosolve®
- Vitreosolve® produces 83% total PVD in NPDR patients
- Vitreosolve® produces vitreolysis and liquifaction in most NPDR patients

UVA -Riboflavin

- 30 minutes of drops and UV radiation exposure
- Strengthen collagen bonds
- Early results are promising as far as corneal integrity improvements but side effects (pain etc.) are relatively unknown and long term data does not exist

Sea Cucumbers:

- Artificial cornea development

Managing Payer Health Systems

1. Patient Information in the future
 - a. Electronic Health Records (EHR)
 - i. HHS directive that all persons shall have an electronic, transferable health record by 2014
 - ii. EHR applications allow for easier management and qualification of levels for E/M coding, which are the major service visits in medical eye care
 - b. All patient information available via Regional Health Information Organizations (RHIOs) now National Health Information Networks
 - i. Be aware of the organizations that are developing in your state
 1. AOA Journal, December 2008, Volume 79, No. 12, pg 746-754
 2. HIMSS State Dashboard www.aoa.org/x652.xml
 - c. E-prescribing
 - i. E-prescribing is being integrated into a number of practice management and EHR systems to facilitate this new mode of Rx transfer and order.
 - ii. E-prescribing bonus is additive to PQRI already in place
 1. 2% bonus calculated against total Medicare payments in 2009-2010, 1% in 2011-2012 and .5% in 2013-2014. Payment reductions are planned in 2015 and beyond for non-E-prescribed Rx
2. Health Systems
 - a. Looking for overall health care cost savings
 - i. Avoiding duplication of services
 1. Referral of patients for care beyond preventive examinations often results in a second comprehensive eye examination
 - ii. Cost effective providers in each specialty

1. With health care costs continuing to rise, ODs are being viewed as cost effective, quality providers
- iii. Pay for Performance
 1. Physician Quality Reporting Initiative (PQRI) has continued to move forward and will likely be the foundation of quality and reporting programs going forward
 2. Base reimbursements will be frozen or increase very little with professionals expected to “earn” the increases under PQRI type programs
 3. Expect PQRI modeled programs to expand to insurance, managed care and vision plans in the near future
 4. Reporting of Quality and Value measures to consumers is being discussed and requested by employers to allow provider selection
- iv. Disease Management
 1. Use of health care information (ICD-9 diagnosis codes and other patient demographics) to provide assistance and direction to effect improved outcomes and reduce overall health costs
 2. Information obtained by all providers has value
 - a. Measures developed following the integration of dental service information
 3. Many vision plans are requiring “all” ICD-9 be submitted
 4. Expect PQRI measures to emerge around Disease Management participation
- b. Integration of Health/Vision
 - i. Movement by managed health care plans to have vision benefits integrated into their overall offerings
 1. United Health Care-Optum Health (Spectera)
 2. Highmark/Blue Shield of PA-Davis Vision
 3. Anthem/Wellpoint-EyeMed Vision Care
 4. Cigna-VSP
 5. Aetna-EyeMed Vision Care
 6. Humana-Comprehensive Benefits and EyeMed Vision Care
 - ii. Participation on medical benefits network
 1. Independent participation
 2. Participation though vision network