ALLOW OCULAR SURFACE RESTORATION

WITH ADVANCED PROTECTION & HYDRATION

The combination HP-Guar/HA as sodium salt formulation attaches to cells in the corneal epithelium and entraps water to promote hydration and lubrication.

With its unique dual-polymer formula, SYSTANE® HYDRATION Lubricant Eye Drops act as a ‘bandage’ to allow restoration of the damaged ocular surface—with prolonged protection and greater hydration than hyaluronic acid alone.

Recommend SYSTANE® HYDRATION Lubricant Eye Drops and support your patients’ ocular surface health.

ALWAYS READ THE INSTRUCTIONS AND USE AS DIRECTED. PLEASE REFER TO PRODUCT PACKAGING FOR DOSE AND PRECAUTIONS. IF SYMPTOMS PERSIST PLEASE SEE YOUR EYECARE PROFESSIONAL.

Eyelid Lesions - spurn or concern ...

Paul Rosser

What causes cancer?

- Basically malignancy is the result of an inappropriate balance of instructions (genetic information) in certain cells

Characteristics of cancer cells

- Immortalisation – an indefinite proliferative life span
- Transformation – loss of normal regulation of cell growth
- Metastasis – the ability to leave the tumour and invade other distant tissues
Fun Facts

• Up to 10% of all skin cancers arise on the eyelids
• Over 90% are on the lower lid
• Over 90% are BCCs
• Approx 5% are SCCs
• 1-2% are melanomas

Skin Cancers

• Risk factors
  – ‘Personal’
  – Local
  – Systemic

Risk Factors - Personal

• Age
• Gender – males predominate
• Lightly pigmented skin
Risk factors - Local

- UV rays – sun, tanning beds
- Chemicals
- Radiation Exposure
- Previous skin cancer
- Severe skin inflammation or trauma

Risk factors - Systemic

- Weakened immune system
- Basal cell naevus syndrome (Gorlin Syndrome)
- Human papilloma virus (HPV)
- Xeroderma pigmentosum

Prevention of Skin Cancers

- Limit UV exposure
- Slip, slop, slap .. and wrap
- Embrace the shade
- Avoid tanning beds
- Regular skin checks
- Parents – protect your kids
Malignant Melanoma

- Cause 1-2% of skin cancers
- Large majority of deaths from skin cancer
- Rates have been rising over the past 30 years
- Average age at presentation = 62 years
- Not uncommon in under 30’s
  - Especially young women

Melanoma – risk factors

- Age, gender (m), reduced immunity
- UV radiation – maybe different types
  - trunk, legs vs face, arms vs palms and soles
- Moles
- Dysplastic naevi (atypical moles)
- Dysplastic naevus syndrome (FAMMM)
- Congenital melanocytic naevi
- Fair skin and freckles
- Family history of MM

Melanoma - Staging

- TNM
  - T = Tumour
  - N = Nodes
  - M = Metastases
T Categories

- Tumour thickness
  - Breslow measurement <1mm much safer
- Mitotic rate
  - Higher mitotic rate more aggressive
- Ulceration

N Categories

- Sentinel node biopsy
- Spread to local lymph nodes
- Spread to distant lymph nodes
  NB – lymph node spread can be macroscopic or microscopic

M Categories

- No metastasis
- Metastasis to skin or nodes
- Metastasis to lungs
- Distant metastasis
- Elevated LDH level – signifies tissue damage
Melanoma Treatments

- Gene therapy – family history
- Targeted drug therapies (BRAF gene)
- Vaccines
- Immunotherapy

Immunotherapy

- CTLA-4 is a protein that suppresses the T cell immune response, thereby helping the tumour cells survive – CTLA-4 blocking drugs may reverse this suppression (Ipilimumab)

- PD-L1 is a protein which helps melanomas evade being detected/destroyed – PD-L1 blocking drugs help the immune system recognise the tumour (Pembrolizumab = 'Keytruda')
Wet and Dry AMD – New Therapies
Dr Alison Pereira

What is AMD?

- AMD is a degenerative retinal disease that can cause central vision loss
- AMD is the leading cause of severe vision loss in people over 50 years of age
Neovascular AMD (Wet AMD)

- Wet, disciform, exudative
- Subretinal neovascular membrane
- Subretinal or intraretinal haemorrhage
- Lipid in macula
- Subretinal scar

AMD: an emerging public health problem

- AMD - leading cause of blindness in NZ
- Prevalence increasing
  - population aging
  - actual increase in age-specific incidence
AMD - an inherited disease

Likely that AMD is a genetic disorder with multiple genes influencing the individual’s susceptibility to environmental factors.

Some genetic factors can expedite the disease by 2.8-12.2 years

AMD management

- Stop smoking
  - past and current smokers developed wet AMD 4.9 and 7.7 years earlier than lifelong non-smokers
- Eat green and coloured vegetables
- UV protection
- Observe an Amsler grid to pick early CNV
- Report any visual symptoms, particularly distortion
AMD management

Supplements

- 500 mg vitamin C
- 400 iu vitamin E
- Lutein 10mg
- Zeaxanthin 2mg
- 15mg zinc as zinc oxide
- 2 mg copper as cupric oxide

Natural History of AMD

- Risk of neovascular AMD over 5 years
  - bilateral low risk drusen 1%
  - Bilateral high risk drusen 10%
  - CNV + high risk drusen 50-87%
Management of AMD

- Atrophic
  - no treatment
  - low visual aids
- Lighting
- Magnifying devices
- Techniques for daily living

AMD: strategies for maximum vision

Current treatments for wet AMD
Avastin (bevacizumab)

- FDA-approved for treatment of metastatic colorectal cancer
- Blocks all VEGF isomers
- Initially administered intravenously
- Now four weekly intravitreal injections
- Effective for all lesion types
- Cost-effective

Lucentis (ranibizumab)

- Fab fragment of the "mother molecule" bevacizumab (avastin)
- 95% response rate and up to 33% gained 15 letters or more
- Four weekly injections
- High cost and number of retreatments

Eylea (aflibercept)

- Blocks VEGF and PlGF
- 4 – 8 weekly injections after a 3 month induction
- High cost
- Excellent response rate
IVTA

- Steroids inhibit angiogenesis, fibrotic proliferation and inflammatory activity
- Side effects – raised IOP and progression of cataract

Potential new treatments for wet AMD

- Strategies for improving treatment
  - Find a better anti-VEGF agent
  - Find a better anti-VEGF drug delivery system
  - Explore combination treatment

Finding a better anti-VEGF agent

- ESBA (Alcon)
  - Pan VEGF-A inhibitor
- CEDAR (Allergan)
  - A DARPin (designed ankyrin repeat protein)
  - Novel class of small molecule with a high affinity to anti-VEGF
- Conbercept
  - Anti-VEGF A and B and placental growth factor inhibitor
  - Similar to Eylea
  - May have a longer half life
  - Produced in China
Finding a better delivery system

- **Intravitreal injection**
  - Positive safety and efficacy profile
  - Initial large bolus of drug beyond therapeutic level which then clears rapidly
  - Frequency
  - Associated discomfort

- **Intraocular implants**
  - New approach with an encapsulated cell technology platform
  - Genetically engineered RPE cells that are capable of producing a therapeutic factor
  - Cells are housed within a semipermeable polymer capsule
  - Sutured to the sclera
  - Neurotech NT 503/506 for wet AMD
    - Long acting delivery of Ranibizumab

- **Topical**
  - Less than 5% of a topically applied dose reaches deeper ocular tissues
  - Viscosity enhancers can increase drug contact time
  - Penetration and permeation can be improved using nanotechnology
  - Examples of nanoparticles are nanospheres, nanocapsules, liposomes and nanomicelles
  - A liposomal preparation of bevacizumab has been studied
Exploring combination treatment

- Fovista
  - Anti platelet derived growth factor in combination with anti-VEGF

Dry AMD

- In the early form patients have drusen which indicate that vision loss may occur if disease progresses
- Patients with late, dry AMD develop geographic atrophy (GA) where the photoreceptors in the central retina slowly die over time

Treatment options for dry AMD

- Antioxidant vitamins
- Immune system strategies
- Decreasing vision cell workload
- Protecting the vision cells
- Cell transplantation
- Eye drops
- Gene therapy
Immune system strategies

- Depends on the complement cascade
- Responsible for attack on the retina
- Inhibiting the cascade may reduce the rate of photoreceptor loss

Science 308, 385 (2005)

Genetics Support a Role for Complement in AMD

Complement inhibitors in Clinical Trials

- C3 Inhibitor
- POT-4 (peptide): Potenita - Intravitreal
- APL-2 (peptide): Apellis - Intravitreal
- Anti-C5
- ARC1905/Zimura (aptamer): Ophthotech - Intravitreal
- Eculizumab (mAb): Alexion – Intravenous
- LFG-316 (mAb): Novartis - Intravitreal
- Anti-Factor D
- Lampalizumab (Fab): Genentech/Roche - Intravitreal
Complement inhibitors in Clinical Trials

- Anti-Factor C5:
  - Systemic C5 inhibition (Eculizimab) Ph 2
  - Intravitreal C5 inhibition (Zimura and LFG-316) Ph 2
- Anti-Factor D:
  - Intravitreal APD inhibition (Lampalizumab) Ph 3
- Anti-Factor C3:
  - POT-4 (Ph 2 suspended)

Inhibitor Overview

- Anti-Factor C5:
  - Systemic C5 inhibition (Eculizimab): Ph 2
  - Intravitreal C5 inhibition (Zimura and LFG-316): Ph 2
- Anti-Factor D:
  - Intravitreal APD inhibition (Lampalizumab): Ph 3
- Anti-Factor C3:
  - POT-4 (Ph 2 suspended)

Immune system strategies
- Another approach is to try and inhibit specific immune cells with the oral antibiotic doxycycline
- Decreasing vision cell workload
  - Unfortunately this has a potential degree of night blindness or difficulty in low light (oral drug emixustat)
- Protecting the vision cells
  - "neuroprotection" with an implant releasing brimonidine

Cell transplantation
- Early clinical trials with RPE stem cell transplantation
- Eye drops
  - MC-1101
  - A drug called MacuCLEAR
  - BD topical treatment may increase blood flow to the retina
  - May protect against expansion of GA by providing better nourishment to photoreceptors and removing waste products
• Gene therapy
• Nanopulse laser
  – Under investigation for early AMD with high risk drusen
• Implantable telescope
  – Galileian telescope design
  – Sulcus based mirror design

Trials at Auckland Eye

• Allergan
  – CEDAR trial with a DARPin for wet AMD vs Lucentis
    • 3 study groups
• Alcon
  – Wet AMD study
• Filly
  – Complement factor C3 inhibitor for dry AMD
  – 4 study groups with one group receiving monthly treatment, another group receiving 2 monthly treatment, the third receiving sham monthly and the fourth, 2 monthly sham (2:1)

AMD - Conclusion

• The increasing disease burden due to an ageing population has focused more attention on treatment for both wet and dry AMD
• Some new treatments have made stabilising and even regaining vision a task within reach
• Early referral is vital
Management of diabetic eye disease

Jo Sims

Epidemiology of diabetic retinopathy (DR)

- Increasing incidence of diabetes mellitus
  - 7% people aged > 25 years in NZ
  - rate 3x higher in Pacific Islanders (18%), also higher Maori and SE Asian (MOH 2014)

- In NZ, 30% of people with diabetes have retinopathy
  - 10% develop maculopathy at some stage
  - Sight-threatening eye disease in 10%
  - Most common cause of visual loss in working age population

Increasing incidence of DM in USA
Risk factors for diabetic retinopathy

- Duration of diabetes mellitus
  - Type 1 DM x 10 years: 7-10% have DMO
  - Type 1 DM x 20 years; 25-35% incidence
- Glycaemic control
- Hypertension
- Cholesterol
- Pregnancy, nephropathy

Clinical features of diabetic maculopathy

- Vision unaffected until late
- Microaneurysms: can leak
- Blot haemorrhages

Clinical features

- Exudate
  - lipoprotein accumulations in the inner and outer plexiform layers of the retina
  - Sub-retinal accumulation of exudate can cause photoreceptor damage and sub-retinal fibrosis.
- Oedema
**Relationship between DR and DMO**

<table>
<thead>
<tr>
<th>Degree of diabetic retinopathy</th>
<th>Risk of DME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild NPDR</td>
<td>3%</td>
</tr>
<tr>
<td>Moderate to severe NPDR</td>
<td>40%</td>
</tr>
<tr>
<td>Proliferative DR</td>
<td>71%</td>
</tr>
</tbody>
</table>

**Grading diabetic maculopathy: NZ photoscreening terms**

- **M1**
- **M2**

- **M3:** exudate > 1 DD from fovea
- **M4:** exudate < 1 DD from centre of fovea
Grading diabetic maculopathy

M5 Centre-involving

Other grading systems

- Early Treatment of Diabetic retinopathy study defined Clinically significant diabetic macular oedema (CSMO)
  Any retinal thickening within 500 microns of the center of the macula.
  Hard exudates within 500 microns of the center of the macula with adjacent retinal thickening.
  Retinal thickening at least 1 disc area in size, any part of which is within 1 disc diameter of the center of the macula.

Other terms relevant in clinical practice

- Centre-involving macular oedema
Risk of vision loss

- If CSMO is present, there is a 30% risk of moderate vision loss at 3 years without treatment

Differentiating DMO from other causes of macular oedema

- CRVO/BRVO
- AMD
- Cystoid macular oedema (uveitic, post-operative)

DMO vs. CRVO/BRVO

DMO
- Bilateral, significant asymmetry is rare
- Usually a mix of MAs, blot haems
- Peripheral changes common

BRVO/CRVO
- Almost always unilateral
- Ven(s) dilated
- Absence of microaneurysms
- Flame haems predominate
- BRVO: changes concentrated in sector of retina
Diabetes

CRVO/ BRVO

What is this diagnosis?

DMO vs. AMD

**AMD**
- May have pigment epith detachment
- Other features: drusen, RPE change
- Absence of periph retinal vasc changes or MAs

**DMO**
- No PED
  - (unless co-existent AMD, which may need angiography to explore)
What has caused this appearance?

- Cannot tell from OCT alone
  - Could be DMO, vascular occlusion, or inflammatory/post op CMO
  - Need to examine patient looking for Mas, blot and dot hx, exudate, inflammation, evidence of recent surgery...

DMO vs. cystoid macular oedema

CMO
- May have intraocular inflammation
- Haemorrhage and microaneurysm very rare
- No exudate

DMO
- No cells
- Should see microaneurysms, exudate (ie some other changes to suggest vascular source of leak)
Management of diabetic maculopathy

- No perfect treatments
- Prevention/ modifying risk factors still most important aspect of care
- All people with diabetes should have regular eye checks for retinopathy

Glycaemic control

- Aim: HBA1c below 6.5 to 7.5% (below 58mmol/L)
- Evidence:
  - DCCT, type 1 DM
    - Intensive blood sugar control reduced development of DR by 76%
  - UKPDS, type 2 diabetics
    - 0.9% decrease in HBA1c was assoc with 37% decrease in risk of microvasc complications

Hypertension

- Aim: BP control at or below 140/80mmHg
- Evidence:
  - UKPDS: tight BP control reduced risk of vision loss by 47% at 9 years
Specific eye treatments for sight-threatening disease

• Treatment is only required when there is a risk of losing sight from diabetes
  – Eg Proliferative diabetic retinopathy
  – Maculopathy with risk of decreased central vision
    • Once visual acuity decreases from maculopathy the prognosis is much more guarded

Laser for diabetic maculopathy

• ETDRS showed 50% decrease in risk of moderate vision loss with laser
  • From 30% to 15% at 3 years
• 20% improve vision
• 15% worsen
• Grid laser for diffuse DME
• OR focal laser direct to MAs

Intravitreous injection

• Anti-Vascular Endothelial growth factor
  – Bevacizumab (avastin) – off label indication
  – Ranibizumab (lucentis)
  – Aflibercept (eyelea)

30 gauge needle 50 μl volume  Tuberculin Syringe
**Intravitreal anti-VEGF monotherapy**

- **RISE AND RIDE studies**
  - Patients with centre-involving macular oedema
  - Sham vs ranibizumab monthly for 24/12
  - Rescue laser allowed
- **Results:**
  - 40-50% with IVL gained 3 lines vision
  - Only 2-4% had severe vision loss

**RISE AND RIDE pooled results**

[Graph showing BCVA improvement over time for different groups.]

**BOLT study**

- Intravitreal bevacizumab or laser
- Mean baseline BCVA in each group was 55 letters
- At 12/12:
  - Laser arm: mean BCVA 50
  - Bevacizumab group mean VA= 61 letters
  - Odds of gaining >10 letters were 5 x greater in bevacizumab group
Anti-VEGF vs. laser for DMO

- DRCR.net randomised clinical trial of 691 patients
- Compared:
  - 1. Sham intravit injection plus laser (control)
  - 2. Intravitreal ranibizumab with prompt laser
  - 3. Intravitreal ranibizumab injection with deferred laser
    - Only after 24 weeks in eyes not responding well to ranibizumab alone
  - 4. Intravitreal triamcinolone with prompt laser

Results at 2 years:
- 49% of eyes treated with ranibizumab and deferred laser showed substantial improvement (mean gain 9 letters vision)
- 36% of eyes in control group improved (mean gain 3 letters)

Vision loss at 2 years:
- 3% ranibizumab group
- 13% control group
Anti-VEGF vs. laser for DMO

- Results:
  - Median number of injections:
    - 8-9 in first year
    - 3-4 in 2nd year
    - 1-2 in third year
  - Visual acuity benefits maintained at least to 3 years
  - DRCR.net algorithm: continue treatment while DMO is improving, discontinue when stable, re-initiate if worsens

Restore study: laser vs anti-VEGF

- 345 patients
  - Ranibizumab and sham
  - Ranibizumab AND laser
  - Sham injx and laser
- Number of people gaining 3 lines of vision (15 letters) at 1 year:
  - 22% ranibizumab
  - 8% sham
  - (no additional benefit seen from RBZ + laser compared RBZ monotherapy)

DRCR.net Protocol T

- For eyes with center involved DMO with decreased visual acuity (20/32-20/320)
- Compare one year efficacy and safety of:
  1. intravitreous aflibercept (Eylea®),
  2. intravitreous bevacizumab (Avastin®) and
  3. intravitreous ranibizumab (Lucentis®)
DRCR.net Protocol T

660 patients with diabetic macular edema were randomized
- 2-mg aflibercept (n: 224)
- 1.25-mg bevacizumab (n: 218)
- 0.3-mg ranibizumab (n: 218)

Treatment schedule

- Repeat injections as often as every 4 weeks, protocol specific algorithm, until 24 weeks
- Resume injections if VA or OCT worsened*
- Focal/grid laser: initiated at or after 24 weeks only if persistent DMO not improving after at least 2 injections

*Improved/worsened defined as:
≥ 5 letter change (~1 Snellen line) from last injection, or,
≥ 10% CST change on OCT from last injection

Aflibercept
Bevacizumab
Ranibizumab

<table>
<thead>
<tr>
<th>Mean no of injections</th>
<th>9.2</th>
<th>9.7</th>
<th>9.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one focal/grid laser</td>
<td>37%</td>
<td>56%</td>
<td>46%</td>
</tr>
</tbody>
</table>
Mean Change in Visual Acuity Letter Score, Full Cohort

52 Week Treatment Group Comparison*:
• Aflibercept vs. Bevacizumab P < 0.001
• Aflibercept vs. Ranibizumab P = 0.034
• Ranibizumab vs. Bevacizumab P = 0.12

* P-values adjusted for baseline visual acuity and multiple comparisons

Mean Change in Visual Acuity Letter Score, Full Cohort

Mean Change in Visual Acuity Letter Score, Baseline Visual Acuity 20/50 or Worse

1-Year Treatment Group Comparison*:
• Aflibercept vs. Bevacizumab P < 0.001
• Aflibercept vs. Ranibizumab P = 0.0031
• Ranibizumab vs. Bevacizumab P = 0.21

* P-values adjusted for baseline visual acuity and multiple comparisons

Visual Acuity Outcomes Baseline = 20/50 or Worse

>15 Letter Improvement>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Difference</th>
<th>CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept vs Bevacizumab</td>
<td>+24% to +39%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Aflibercept vs Ranibizumab</td>
<td>+18% to +32%</td>
<td>0.0078</td>
<td></td>
</tr>
<tr>
<td>Ranibizumab vs Bevacizumab</td>
<td>+6% to +19%</td>
<td>0.34</td>
<td></td>
</tr>
</tbody>
</table>
Protocol T conclusion:

- All three anti-VEGF agents are effective treatments for DMO causing vision impairment
- When initial visual acuity loss is mild, on average there is little difference in visual acuity at 1-year
- At worse levels of initial visual acuity aflibercept is more effective at improving vision

Issues with anti-VEGF

- Huge burden on public health system
- Cost
- Long term safety?

- Currently: Mainly reserved for central oedema

Intravitreal triamcinolone

- Long acting steroid
- Smaller role now
- Increased complications
  - IOP
  - Cataract
- Can still be useful for severe macular oedema or intraoperatively
Ozurdex implants

- Phase 2 and 3 trials have shown increased VA and decrease CMT
- Risks of cataract, glaucoma, and increased infection risk
  - Mostly used in VEGF-resistant, pseudophakic, vitrectomised

Role of vitrectomy

- Can be useful if significant epiretinal membrane or traction
- Often have trial of anti-VEGF before surgery

Patient 1: diabetic 10 years, HbA1c 101

“would rather be blind than fat”

October 2015: R3, M2 both eyes
Summary of DR

- 1st and 2nd prevention very important, co-manage with diabetes physician
- Regular monitoring of “at risk” people
- Treatment when indicated
  - Good evidence to support anti-VEGF for centre-involving DMO
  - Improving outcomes
  - No 100% cure