Research Review Speaker Series

ANZSRS Retina Symposium

Australian and New Zealand Society of Retinal Specialists (ANZSRS) Retina Symposium

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Abbreviations	
AMD	age-related macular degeneration
BRVO/CRVO/HRVO	branch/central/hemicentral retinal vein occlusion
CI	confidence interval
CNV	choroidal neovascularisation
CSC	central serous chorioretinopathy
DMO	diabetic macular oedema
DRCRnet	Diabetic Retinopathy Clinical Research Network
ERM	epiretinal membrane
(F)FA	(fundus) fluorescein angiography
GWAS	genome-wide association study
ICG	indocyanine green
ILM	internal limiting membrane
IOP	intraocular pressure
MFS	myopic foveoschisis
MI	myocardial infarction
NNT	number needed to treat
OCT	optical coherence tomography
OR	odds ratio
PED	pigment epithelial detachment
PDT	photodynamic therapy
RCT	randomised controlled trial
RPE	retinal pigment epithelium
RVEEH	Royal Victorian Eye and Ear Hospital
SRF	subretinal fluid
VA	visual acuity
VEGF	vascular endothelial growth factor

Welcome to this review of the Australian and New Zealand Society of Retinal Specialists (ANZSRS) Retina Symposium, held August 27–28, 2011 in Sydney, NSW. Presentations made at the symposium have been summarised for your information.

Neovascular age-related macular degeneration

Summary of trial results – safety and efficacy

Presenter: Dr Jennifer Arnold

CATT trial

The US NEI-funded CATT noninferiority trial randomised 1208 patients with new untreated active CNV from AMD (VA 20/25–20/320; 53–61% with subfoveal CNV; <50% lesion area fibrotic) to ranibizumab (Lucentis) 0.5mg or bevacizumab (Avastin) 0.25mg either as needed (without a loading dose; driven by any change on OCT) or monthly for 2 years; half the participants in the monthly arms were rerandomised to monthly or as needed for year 2.[CATT] The 12-month results showed no significant differences between the four arms for improvements of ≥5 letters in VA, but there was a trend for higher rates in the monthly arms versus the as-needed arms (31.3–34.2% vs. 24.9–28.0%); the two as-needed arms also received significantly fewer injections than the monthly arms. Noninferiority, defined as a VA change of 5 letters with a CI of 99.2, was demonstrated for all comparisons except bevacizumab as needed versus monthly and bevacizumab as needed versus ranibizumab monthly. Ranibizumab monthly was associated with a significantly greater reduction in mean retinal thickness compared with the other three groups (196 vs. 152–168µm; p=0.03), and although absence of fluid on OCT was also reported in significantly more participants, the proportions were still quite high (43.7% vs. 19.2–26.0%; p<0.001).

Eight other trials are currently ongoing, most notably: i) the 2-year UK IVAN trial (n=600), which has a similar design to the CATT study; ii) GEFAL (n=600) in France; and iii) VIBERA (n=360) in Germany.

Ranibizumab versus bevacizumab

While ranibizumab and bevacizumab are similar in many ways, there are differences with regards to their biochemical profiles that have both clinical and safety implications.[Meyer 2011] Ranibizumab (a Fab fragment only) neutralises VEGF at lower concentrations, has greater retinal penetration and potency and does not cross into the systemic circulation. Bevacizumab (a full-length antibody) is able to cross into the systemic circulation and can have a greater effect on the fellow eye. Particulate matter in compounded bevacizumab increases its degradation and could also reduce its efficacy, and there is also emerging evidence that IOP and inflammation are increased.

Safety of anti-VEGF agents

Anti-VEGF agents are known to slow wound healing and new blood vessel growth, and there is a theoretical risk of arterial thromboembolic events. US Medicare analyses of large numbers of patients with AMD have shown significantly increased risks of mortality and stroke associated with bevacizumab versus ranibizumab use, but no increased risks of MI and ischaemic stroke.[Curits 2010, Gower 2011] Gower et al also found that bevacizumab was associated with significantly increased risks of ocular inflammation and cataract surgery and a lower risk of newly diagnosed ocular hypertension/glaucoma. However, a recently published smaller analysis of US veterans showed no significant increased risk of mortality associated with anti-VEGF treatment.[French 2011] While the CATT study is underpowered to detect increases in stroke risk, the available data suggest a (nonsignificant) increased risk of death among bevacizumab recipients (15 vs. 9 participants) and a significantly higher rate of ≥1 systemic adverse event (p=0.04), particularly GI disorders (p=0.02).[CATT]

Safety conclusions

- Known association between AMD and cardiovascular disease
- Bevacizumab may be associated with higher risks of mortality and haemorrhagic stroke than ranibizumab
- Clinical trials recruit 'well' people with a lower adverse event rate than the general population
- Claims data suggest rate of death and cardiovascular disease is low

New anti-VEGF agents

Aflibercept ophthalmic solution (VEGF Trap-Eye) is a fusion protein that blocks VEGF-A and -B plus placental growth factor, and has very high affinity, good retinal penetration and long duration of action. The ongoing VIEW 1 and 2 studies investigated noninferiority of aflibercept 0.5mg every 4 weeks (n=597), 2mg every 4 weeks (n=613), or 2mg every 8 weeks after three monthly loading doses (n=607) versus ranibizumab 0.5mg every 4 weeks (n=595) for preventing vision loss ≥15 letters (primary outcome) in patients with AMD. Twelve-month data showed that the primary outcome rates were similar with the three aflibercept doses and ranibizumab (95.3–96.1% vs. 94.4%) as were the proportions of participants achieving a ≥15 letter gain (29.8–33.4% vs. 32.4%), changes in retinal thickness and adverse event rates.

Panel Discussion

Moderator: Jennifer Arnold

Panel: Paul Beaumont, Samantha Fraser Bell, David Squirrel

The Panel discussed the following dilemmas associated with AMD therapy.

Treatment paradigm – monthly versus as needed as either: i) withhold until disease activity with monthly review; or ii) treat and extend

Summary data from the various studies show that VA improvements continue after induction is complete when patients are treated monthly, while decreases are seen after induction when patients are treated as needed. However, this latter trend was reversed in the as-needed arm of the CATT study, but this was likely due to differences in the 'rules' of when to treat based on OCT findings. The panel members noted that demographics can influence the choice – e.g. patients may be lost to follow-up if treatment periods are long. Also patient preferences should be taken into account, and these can be influenced by the relative function in the treated eye compared with the fellow eye.

Induction phase

The general consensus among the panel members was that three monthly induction injections are valuable.

Retreatment criteria

Commonly used retreatment criteria are: i) VA decrease >5 letters; ii) OCT shows change in centre point thickness of 100µm or any fluid; iii) new or persistent blood; and iv) leakage on FA. It may still be possible to extend treatment if a small amount of persistent blood is present and other clinical parameters are good.

Diagnosis and monitoring tools

Panel members usually restrict monitoring tools to VA, fundus examination and OCT. It was generally felt that angiography provides little useful information for monitoring in most patients, but there are a few patients in whom it is valuable (e.g. when considering extending treatment of better eye).

CNV classification

CNV classifications are useful to consider when making treatment decisions. They have been refined with anatomical location using OCT with or without ICG angiography, and they are summarised nicely in an editorial by Freund et al.[Freund 2010] Most seen in clinical practice are sub-RPE (type 1), while others include subretinal (type 2) and intraretinal (type 3). Type 2 CNV often responds well to anti-VEGF treatment, type 3 can be difficult to treat, while responses in type 1 can be variable.

Nonresponders – is a 'dry' ICT a realistic aim?

How 'fluid' is defined was discussed, with particular reference to the CATT trial data, where 25–30% of cases that the trial's reading centre regarded as having fluid were not judged to be important fluid by the treating investigator.

Endophthalmitis update – focus on intravitreal injections

Presenter: Penny Allen, RVEEH

Data show that the incidence of injection-related endophthalmitis is very low (table 1). Data from the RVEEH show that while there was only two cases of ranibizumab injection-related endophthalmitis in 2007–9 (17,639 injections), there were 9 cases in 2009–10 (18,948 injections) with a further nine cases from 2010 to the end of June 2011 (number of injections not available). Of the 18 cases over the last 2 years, all but two were culture positive, mostly coagulase-negative staphylococci. This is consistent with a meta-analysis reporting that 65.4% of 26 culture-positive cases from 105,536 injections were coagulase-negative staphylococci.[McCannel 2011] This meta-analysis also found that 30.8% were streptococci, which is higher than expected postoperatively, and notable incidences of streptococci cases have also been reported in retrospective analyses.[Moshfeghi 2011, Mezad-Koursh 2010]

Table 1. Incidences of injection-related endophthalmitis in trials

Agent	Source	Incidence (per injections)
Ranibizumab	DRCRnet laser	0.09% (3/3226)
Triamcinolone	DRCRnet laser	0% (0/612)
	DRCRnet DME and SCORE	0.05 (1/2009)
Bevacizumab	Israel 2006–2008	0.07% (2/2789)
	Miami 2005–2010	0.018% (7/3970)

Features of endophthalmitis cases at the RVEEH have been typical (i.e. presentation ≤3 days postinjection, more aggressive than postoperative disease, blurred vision, pain, hypopyon, fundal view loss, streptococci common, and visual outcomes often poor and dependent on cultured microorganism). The point was made that streptococci are relatively common in oral flora, suggesting possible transmission from the individual administering the injection. Proposed preventive measures outlined were: i) povidone-iodine preparation; ii) use of lid speculum; iii) minimise speaking to patient; iv) use of a mask; and v) avoid pre-injection antibiotics. There is no evidence supporting the use of postinjection antibiotics. The presence of a viral infection may also lead to increased bacterial shedding. Patients should be educated and warned of symptoms, and prompt treatment with appropriate intravitreal antibiotics (e.g. vancomycin for gram+) with or without dexamethasone or early vitrectomy for more aggressive cases.

Ongoing projects at the RVEEH include: i) culturing conjunctiva of fellow eye and nose; ii) PCR for all cases, particularly after intravitreal triamcinolone, which tend to be more likely to be gram– cases; and iii) survey of all ophthalmologists in Victoria regarding injecting practices.

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Central Serous Chorioretinopathy

Current understanding of CSC

Presenter: Alex Harper

The term CSC is probably more accurate than the UK variant CSR (central serous retinopathy). Acute CSC implies fluid with minimal RPE changes, while chronic CSC is associated with extensive RPE changes with or without SRF, but there is overlap between them (e.g. acute-on-chronic CSC, persistent acute CSC). Small serous PEDs usually precede symptoms.

Clinical features of acute CSC include serous retinal detachment, RPE leak on FFA (often from PED), and fibrin exudates in 10%. The choroidal dysfunction pathogenesis theory is supported by fibrin in SRF secondary to marked changes in choriocapillaris permeability. Such changes result in focal loss of adhesion between RPE and Bruch's membrane, leading to a focal break in the RPE allowing protein and fluid to enter the subretinal space.

Vision loss also correlates with OCT findings in chronic CSC. It is easily recognisable, with possible features including retinal thinning with loss of IS/OS, cystoid macular degeneration and SRF.

Corticosteroids (exogenous and endogenous) can exacerbate CSC or prolong its course, although the biological basis for this is uncertain. There is an emerging association between sleep apnoea and CSC. While little genetic research has been done, familial clustering is seen, and GWASs are needed.

Treatments for CSC

Presenter: Rohan Merani

A number of questions remain unanswered regarding CSC treatment. Initial management of CSC is usually observation, as it is often self-limiting and improves without any intervention, particularly when corticosteroid exposure, sleep apnoea, uncontrolled hypertension and stress have been addressed. Treatment of acute CSC is generally only considered if the patient's occupation is dependent on good vision or if the fellow eye is known to have poor vision. While the best time to offer treatment has not been defined, treatment by 3 months is generally considered prudent before permanent visual deficits emerge, but quicker resolution could reduce symptomatic distortion or recurrence.

Studies have shown that laser treatment accelerates resolution, but the findings regarding recurrence and final VA have been mixed.[Leaver 1979, Ficker 1986, Robertson 1983, Burumcek 1997] It is believed that laser debrides RPE and stimulates adjacent RPE cells to slide over and close the defect.

PDT is usually the preferred interventional treatment for CSC, as it targets choroidal problems. The results of initial studies were not remarkable,[Yannuzzi 2003] and this may be explained by the extensive disease in the participants or by the use of full-dose PDT, which could result in: i) RPE atrophy; ii) choriocapillaris ischaemia/hypoperfusion; iii) secondary CNV; or iv) transient reduction in macular function. Various studies have shown that reducing the verteporfin dose or fluence in both acute and chronic CSC is as effective as full-dose therapy while minimising deleterious effects.[Chan 2008a, Chen 2008b, Shin 2011, Zhao 2009, Inoue 2010, Maruko 2010] Unlike laser, PDT also reduces choroidal thickness, suggesting it is targeting the pathophysiology of the disease.

Study results for bevacizumab in CSC have shown initial improvements, but recurrence has been a problem.[Schaal 2009, Lim 2010] More encouraging results with a single injection of double-dose bevacizumab have been reported in one nonrandomised study, but other studies to support these results are lacking.[Artunay 2010]

No studies investigating ranibizumab in CSC have been published. Other treatment options (micropulse diode laser, mifepristone, acetazolamide and β-blockers) have limited evidence and require more study.

General points from panel discussion of CSC cases

Moderator: Alex Harper

Panel: Jennifer Arnold, I-Van Ho, Rohan Merani

- Risks of laser are very small, and it can be helpful
- Vision decreases with PDT are under-reported in the literature – patients with a lot of subretinal fibrin are particularly at risk
- Polyps can masquerade as CSC
- CSC affects mostly males with a ratio of about 10:1
- Choroidal folds can be associated with CSC
- Chronic cystoid degeneration is a marker of nonresponse

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Diabetic macular oedema

Summary of trial results

Presenter: Prof Paul Mitchell

Contemporary trials highlight two unmet medical needs of DMO, with mean vision changes seen with laser ranging from –4.6 to +3 letters, and as many as 26% of participants experiencing a loss of ≥3 lines.[DCRnet 2010, Michaelides 2010] Fenofibrate reduced the need for laser therapy by 30% and 40% (NNTs 14 and 27) in the FIELD and ACCORD studies, respectively.[Keech 2007, ACCORD] However, the effects were not related to blood lipid levels, and it has been suggested that fenofibrate has anti-VEGF properties. As such, fenofibrate could be recommended in guidelines for patients with early retinopathy.

Anti-VEGF agents represent a major advance in the treatment of DMO, with no other treatments meeting the two unmet medical needs. Among the anti-VEGF trials, ranibizumab with prompt laser, ranibizumab with deferred laser, triamcinolone with prompt laser and sham injection with prompt laser were compared in 854 eyes in DRCRnet. Two-year results showed significantly better outcomes in the ranibizumab arms compared with the sham and triamcinolone arms, but ranibizumab recipients with deferred laser fared better than those with prompt laser by a couple of letters.[DRCRnet 2010] Similarly, the 12-month results from RESTORE showed no benefit of adding laser to ranibizumab.[Mitchell 2011] Furthermore, monthly ranibizumab 0.5mg injections (with rescue laser) were associated with significant improvements of 9.7–10 letter gains over 2 years compared with sham injections in the RIDE and RISE studies, with evidence of continued improvements during the second year.[Business Wire] The DA VINCI and BOLT studies showed that aflibercept and bevacizumab, respectively, also improved vision compared with laser, with improvements also appearing to continue beyond the first year in DA VINCI.[Michaelides 2010, Do 2011]

Anti-VEGF therapy has consistently been associated with vision improvements in ~3 times as many study participants as seen with laser alone, and the anti-VEGF recipients were also less likely to experience vision loss.[DRCRnet, Michaelides, Mitchell, Do, Massin 2010]

Questions remaining regarding anti-VEGF therapy include: i) when to start? ii) what characteristics suggest it is not working and should be stopped? iii) are there predictors of response? iv) how should treatment be initiated? v) what are appropriate injection intervals? vi) what are the indications to stop? vii) what are the retreatment criteria? and viii) is it safe?

There is now a strong argument that anti-VEGF agents be used for first-line DMO therapy. RESTORE trial data show that: i) outcomes with anti-VEGF therapy between focal and diffuse DMO cases are similar, and not affected by laser therapy; and ii) while vision improvements are better when the retinal thickness is >400µm, quality of life gains are greatest in those with the least vision impairment before treatment (i.e. retinal thicknesses ≤400µm) as such patients are more likely to experience restoration of 'normal' vision.[Mitchell 2011]

Data to date support the safety of anti-VEGF therapy; however, as these patients have diabetes mellitus, vigilance should be maintained regarding cardiovascular risks.

General points from panel discussion of DMO cases

Moderator: Paul Mitchell

Panel: Alex Harper, Mark Gillies, Brendon

- There are currently no guidelines for the most used anti-VEGF bevacizumab, but trial data indicate that treatment needs to be continued for ≥12 months, rather than 2–3 treatments.
- Classification of DMO that includes OCT findings is needed.
- Patients with ischaemia don't appear to get worse with anti-VEGF therapy, but there are no good data supporting reversal of existing macular ischaemia.
- If anti-VEGF is to be considered prior to surgery (e.g. proliferative retinopathy), procedure should be performed in 2–4 days – detachment can develop if left.
- Two algorithms exists for anti-VEGF therapy:
  - RESTORE-like initiation and interruption – monthly injections until maximum VA is achieved, and resumed if VA loss occurs during monthly monitoring.
  - DRCR.net-like – 4 × 4-weekly injections, followed by 2 more if not successful (VA 20/20 or OCT central subfield thickness <250µm), and seven additional injections if improvement (OCT central subfield thickness decreased ≥10% or VA improved by ≥5%), but not 'success', otherwise optional; could extend to 8 or 16 weeks during second year.
- The general consensus of the panel was to treat patients on a case-by-case basis, considering the impact of the commitment of treatment.
- Assessment of improvement should involve both VA and OCT.
- More work needs to be done on predictors of response.
- Interest was expressed for a study of micropulse laser versus anti-VEGF.

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Retinal Vein Occlusions

Summary of trial results

Presenter: Anthony Kwan (Queensland Eye Institute and Mater Hospital, Assoc Professor of Ophthalmology, University of Queensland, Brisbane)

Treatment for CRVO and BRVO changed significantly in 2009, and since then a number of relevant RCTs have been published (Table 2). Analysis of results from the trials found NNTs for CRVO of 3, 5 and 17 for ≥15-letter gains at 6/12 months for ranibizumab 0.5mg, triamcinolone 4mg and dexamethasone 0.7mg, respectively, and the respective rates of vision loss of ≥15 letters were 2% (vs. 15% for sham), 25% (vs. 44% for observation) and 6% (vs. 11% for sham). For BRVO, the respective rates of ≥15-letter gains for ranibizumab 0.5mg, triamcinolone 4mg and dexamethasone 0.7mg were 61% (vs. 29% for sham; NNT 3), 26% (vs. 29% for grid laser) and 23% (vs. 20% for sham; NNT 17), and the respective rates versus sham/grid laser for ≥15-letter losses were 2% vs. 5%, 12% vs. 15% and 6% vs. 11%. The COPERNICUS and GALILEO trials are investigating aflibercept, which has yet to be approved, versus sham in CRVO. There are a number of other trials, e.g. comparing different doses of anti-VEGF agents and treatment of ischaemic CRVO.

When choosing treatment, consider: i) tailoring to the individual; ii) extrapolate trial results cautiously; iii) monitor all individuals with capillary nonperfusion and neovascularisation; iv) observation in willing patients (chance of spontaneous improvement); v) combination treatment (e.g. laser plus anti-VEGF in BRVO); and vi) rebound VEGF levels result in neovascularisation when anti-VEGF treatment ceases.

Table 2. **Recent RCTs of RVO treatments**

Design	Summary results
SCORE	
Triamcinolone 1mg or 4mg vs. standard care in: CRVO (vs. observation)[Ip]	≥15-letter VA gain: 27% (1mg) and 26% (4mg) vs. 7% (p=0.001 for both) with improvements apparent from 4– 24mo IOP/glaucoma: 20% and 35% vs. 8% (p=0.02 and <0.0001, respectively, and 0.02 for 1mg vs. 4mg)
and BRVO (vs. laser)[Scott]	Some improvements in all 3 arms at 1yr with no between-group differences, but laser superior by 3yr
Geneva	
Intravitreal dexamethasone implant 700µg vs. sham in CRVO and BRVO for 6mo[Haller 1]	Time to achieve 15-letter VA gain was significantly shorter for active treatment than sham treatment in both CRVO and BRVO from d20–90 (peak d60), with no difference at d180 Dexamethasone reduced 15-letter loss by 50% compared with sham treatment Efficacy persisted at 12mo in 17% and 21% of CRVO and BRVO participants, respectively IOP in 25% vs. 1% in sham treatment
Extension to 12mo – dexamethasone reinjections in both arms[Haller 2]	VA improved again after second injections 32.8% of dexamethasone retreated participants had ≥10mm Hg increase in baseline IOP; disappeared after d180 and responded to usual treatment Cataract development occurred in 29.8% of retreated participants and 10.5% of previous sham treatment participants
BRAVO	
Ranibizumab 0.3mg or 0.5mg monthly vs. sham injection for 6mo, followed by ranibizumab PRN for 6mo for all participants (observation), for BRVO or HRVO; rescue laser available months 3–6 or 9–12[Campochiaro 1, Brown 1]	VA and anatomical improvements evident from d7 in ranibizumab arms Both letter gain and % eyes with ≥15-letter gains at 6mo better with ranibizumab than sham (18.3 vs. 7.3 letters and 61% vs. 29% of eyes, respectively), and maintained to 12mo in the ranibizumab arms VA gains in initial sham group participants who crossed over to ranibizumab at 6mo were not as great as those from the initial ranibizumab arm Observation period ranibizumab safety findings consistent with initial ranibizumab group
CRUISE	
Same as BRAVO in CRVO (no rescue laser) [Brown 2, Campochiaro 2]	≥15-letter gains better with ranibizumab 0.3mg and 0.5mg vs. sham at 6mo (46.2% and 47.7%, respectively, vs. 16.9%; p<0.001 for both); not significantly different at 12mo (47.0% and 50.8%, respectively, vs. 33.1%) Observation period ranibizumab safety findings consistent with initial ranibizumab group

General points from panel discussion of RVO cases

Moderator: Anthony Kwan

Panel: Wilson Heriot, Ian McAllister, Paul Beaumont

- Consensus was that aspirin/anticoagulants provide little or no benefit
- Consider rescue laser if oedema persists after anti-VEGF
- Avoid anti-VEGF therapy for at least 5 weeks prior to anastomosis, and wait until it develops before restarting anti-VEGF therapy
- A more sophisticated approach is needed that addresses all components in RVOs, including venous hydrostatic pressure, endothelial barrier breakdown and upregulation of VEGF

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Vitrectomy in eyes with medical retinal conditions – pros and cons

Presenter: Prof Philip Polkinghorne MD FRANZCO (Assoc Professor, Faculty of Health Sciences, University of Auckland, NZ)

There are limited studies on vitrectomy for retinal medical diseases, due to mainly being used when other treatments are unsuccessful. This presentation was limited to the following three topics.

1. DMO

Evidence suggests that vitrectomy has some role to play in DMO, but the questions of 'what to do?' and 'what works?' still remain. The 3-year results of the Early Treatment Diabetic Retinopathy Study (improvement of ≥3 lines in <3% and vision loss in 12%[ETDRS]) prompted vitreous surgery to be considered as an alternative. Many papers were subsequently published during the 1990s describing various vitreous surgeries (vitrectomy, ERM peel, ILM peel) in DMO, and while they resulted in improvement on imaging, what they achieved was still not clear. In the DRCR.net trial published in 2010, 12% of participants ended up undergoing vitrectomy for treatment failure or diabetic retinopathy complications.[DRCR.net] DRCR.net then reported outcomes in 241 eyes with DMO and traction treated with vitrectomy with or without: i) ERM peel; ii) ILM peel; iii) intravitreal corticosteroids; and iv) PRP.[Flaxel] Worse baseline thickness predicted improved final VA and decreased macular thickness, ERM removal predicted improved final VA only, and ILM removal and presence of traction predicted decreased macular thickness only.

2. CRVOs/BRVOs

There is little scientific evidence regarding the role of vitrectomy in CRVOs and BRVOs, although some believe it may have a role when traction is present – the general conclusion was that of a potential, limited role.

3. Vitrectomy and pharmacokinetics of intravitreal medications

Clearance of intravitreal antibiotics and triamcinolone is increased following vitrectomy, while dexamethasone implants (Ozurdex) are not affected.[Iyer, Kosobucki, Chang-Lin,] While clearance of anti-VEGF agents is also increased after vitrectomy, clearance of VEGF itself is also increased, so the overall effect is probably neutral.[Lee, Seo, Aiello]

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Myopia

Prevalence and pathogenesis

Presenter: Prof Paul Mitchell, MD PhD FRANZCO FRCOphth (Professor, Department of Ophthalmology, University of Sydney, Westmead Millennium Institute, Westmead Hospital, Sydney)

Myopia risk factors include: age (hyperopic vs. myopic shift for <65 vs. >65 years); gender (higher prevalence among women for high myopia); ethnicity (highest in East Asia, then South Asian; lowest in Blacks, Hispanics and Caucasians); genetics; near-work; education; and others.[Attebo, Wong, Kempen] Evidence for cohort effects on risk has been seen in both ethnic and age (younger and older) groups. The highest prevalences among Asian countries appear to be in those with the greatest education pressures, particularly in East Asia. Evidence is also emerging from a number of countries for an age shift in axial length. An analysis of 124 East Asian children aged 7 years from the Sydney Myopia study versus 628 matched children from the Singaporean SCORM study found: i) a significantly lower myopia rate (3.3% vs. 29.1%; p<0.0001); significantly shorter axial lengths (22.60 vs. 23.13mm; p<0.0001); and iii) very similar parental myopia rates.[Rose] A multivariate analysis showed that the highest risk was in children with low and high amounts of outdoor activity and near-work, respectively. Beaver Dam Eye Study data showed an increased prevalence of myopia in more recent birth cohorts,[Lee] and this is being seen in other countries with high levels of education. There are few data on high myopia, but evidence from Singapore has shown that its prevalence has increased along with myopia.

Myopia is associated with costs (refractive correction and surgery) and morbidity from contact lens wear, retinal detachment, myopic retinopathy, macular degeneration, other myopia-related retinal diseases, increased risk of glaucoma, earlier-onset, increased PSC cataract and cataract surgery. Myopia is now ranked in the top 5–6 causes of blindness, most frequently due to myopic retina degeneration. There is a linear relationship between the prevalence of signs of myopia (lacquer cracks, Fuch's spot, chorioretinal atrophy, staphyloma) in the community and both spherical equivalents and axial length. A large, recent Singaporean GWAS found only two SNPs on chromosome 5p15 in one gene *(CTNND2)* to be strongly associated with the development of myopia.[Li]

Myopia increases the risk of: i) cataracts (adjusted OR 2.5 [95% CI 1.6–4.1]) and requiring cataract surgery (3.4 [1.0–11.3]);[Lim,Younan] ii) glaucoma (2.3 [1.3–4.1] and 3.3 [1.7–6.4] for low and high myopia, respectively);[Mitchell] and iii) incident visual impairment (>6/12; 1.26 [1.14–1.39]) and blindness (>6/60; 1.20 [1.06–1.35]). The risk of peripapillary atrophy is increased as spherical equivalent increases.

Recent imaging advances for high myopes

Presenter: Dimitri Yellachich

While choroidal imaging has always been possible with OCT, obtaining a good image of a healthy retina has been difficult. Enhanced depth imaging OCT, based on pushing the OCT closer, provides better imaging of superchoroidal space and even vessels in the sclera. It has allowed quantification of choroidal thickness, which decreases with age and is decreased in myopia. OCT has allowed the identification, and in many cases better categorisation/classification, of entities such as: i) dome-shaped macula; ii) peripapillary intrachoroidal cavitation (previously thought to be an RPE detachment); and iii) MFS and its classification (foveal detachment, foveal retinoschisis, macular hole, lamellar hole). Autofluorescence can be useful for retinoschisis, but only if it is correlated with OCT. Some changes on OCT can illustrate traction involved in the aetiology of retinoschisis, e.g. tractional ILM detachment, vascular microfolds and, prior to retinoschisis, paravascular retinal cysts and paravascular lamella holes.

Developments in OCT technologies include:

- Spectroscopic OCT
- Faster image acquisition
  - Swept source – higher pixel density, significantly faster
    - En face
- Adaptive optics
  - Increasing transverse resolution
- Doppler OCT
  - OCT angiography
- Functional OCT
- Polarisation sensitive OCT
- Magnetomotive OCT – dynamic magnetomotion of magnetic nanoparticles detection, labelled molecules

Myopic CNV – diagnosis and treatment

Presenter: Dr Mark Gorbatov (Vitreoretinal Surgeon, Retina and Vitreous Centre and Sydney Eye Hospital)

Pathological myopia is one of the second most common causes of CNV. Presenting patients are myopes or ex-myopes with symptoms of macula disease. The diagnostic aims are to determine if CNV is present, and if so, is it degenerative myopia. Diagnosis is typically based on clinical presentation, OCT and FA; ICG and fundus autofluorescence have limited diagnostic value. A low threshold for angiography was recommended. Compared with AMD, clinical features of CNV include younger population, short duration with relatively good vision and small lesions.

Prior to anti-VEGF therapy, treatment was mainly thermal laser and PDT, with submacular surgery moderately successful with type 2 anatomy of new vessels. Bevacizumab took over from PDT as the main treatment when it became available. Other pharmacotherapy options include orbital or intravitreal corticosteroids and ranibizumab.

The VIP study showed that loss of vision (primary endpoint) was significantly lower with PDT than placebo at 12 months, but not at 24 months,[Blinder] while a case series reported that 12/13 subfoveal myopic CNV eyes had atrophy and VA loss between 4–5 years of follow-up, while 5/7 juxtafoveal eyes had not.[Hayashi] A number of case series have demonstrated the efficacy of anti-VEGF agents in myopic CNV. One RCT comparing PDT, laser and bevacizumab in juxtafoveal myopic CNV showed that over time there was deteriorating, stable and improved vision with the three respective modalities.[Parodi] Another recent, small RCT found no difference in improvements between bevacizumab and ranibizumab.[Gharbiya] Combining anti-VEGF therapy with PDT is no better than anti-VEGF monotherapy; no studies have investigated anti-VEGF therapy plus thermal laser. Studies of triamcinolone plus PDT have reported variable findings, but one study in patients with AMD, myopic and idiopathic CNV reported a VA benefit of the combination over PDT alone that was driven by myopic participants.[Lee] The presenter's own observations that older patients receive more treatment and have worse vision are reflected in natural history data from the literature, but there is yet to be an age effect seen in studies on anti-VEGF agents.

Animal studies have shown that high systemic doses of anti-VEGF agents during pregnancy can cause pregnancy loss, intrauterine growth retardation and teratogenesis. No adverse effects occurred in six case reports of women receiving 17 doses of intravitreal bevacizumab, including three during the first trimester, but one report has described miscarriage in two separate women 7–10 days after they received intravitreal bevacizumab during early pregnancy.

Myopic macular surgical complications

Presenter: I-Van Ho (Sydney Eye Hospital; Head of Vitreoretinal Surgical Fellowship, ASAM Macquarie University Ophthalmology; Head of Ophthalmic Surgery Retina Associates)

Elongation and bulging result in mechanical changes in the retina that indicate surgery. A large series of 522 patients with pathological myopia over 10 years found that age (≥6/12 outcome in 92% for 40–49 years vs. <40% for >60 years), macular pathology (≥2 line loss in 50%, vs. 4.3% for no macular pathology), refractive status and axial length predicted worse outcomes.[Shih]

MFS affects 9–34% of highly myopic eyes with posterior staphyloma, and 50% progress to macular hole or retinal detachment in ≥2 years.[Panozzo, Takano, Shimada] Globe elongation, vitreoretinal interface (cortical vitreous plaques), retinal vessel traction and ILM rigidity and contraction (which is an active progressive process) all contribute to the pathogenesis of MFS. MFS is staged from 0–5, with 50% of stage 0 cases progressing through stages 1–4. Progression to stage 4 typically takes around 6 months, but vision loss does not usually occur until stage 4.

Only small studies on management options for MFS have been published (Table 3). Dr Ho's approach is to observe during stages 0–1, use vitrectomy, ILM peel and/or gas for stages 2–4 or macular hole, and vitrectomy and gas for retinal detachment.

Table 3. Summary findings of studies investigating the management options for MFS

Better preoperative BCVA, axial length (<28mm) and foveal detachment were predictors of better outcome for ILM peeling.[Kumagai]
Surgery after macular hole developed was associated with only a 25% primary closure rate, and none of the failures closed after reoperation; BCVA improved in 37.5%, and worsened in 25%.[Ikuno]
Macular buckling – no agreed technique, standard of care before 1982, but renewed interest since 2007 for macular hole retinal detachment not repairable with vitrectomy.

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MacTel update

Presenter: Mark Gillies

The MacTel project has been running for 6 years in 25 centres worldwide, with the aims of: i) identifying the causes of macular telangiectasia; and ii) explore potential treatments. The clinical centres follow patients in a natural history study, and there are also four laboratories and genetics, reading and co-ordinating centres.

Macular telangiectasia is more common than believed (~1 in 1000) and it affects people worse than previously thought. Systemic associations with diabetes and vascular risk factors have been identified, and early specific autofluorescence changes are seen. The causes are still not known, but it is currently thought it could be a primary Müller cell defect – nearly all the features of the disease can be replicated by knocking out Müller cells. Strong familial associations are apparent, and although no defective gene has yet been identified, a whole genome analysis is currently being conducted.

No treatment has been established. Laser has not been helpful. Anti-VEGF therapy for subretinal neovascularisation can be helpful, but non-neovascular generalised leaks recur, and blind spots may develop, after initial resolution with anti-VEGF therapy. A neurotrophic factor secreted by Müller cells has been shown to reduce photoreceptor death in mice, and a safety study in eight patients is underway, with preliminary plans for an efficacy study early in 2012.

Zebra hunters – presentations of 'rare and wild' cases

i) ARPE in a 16-year-old male

ii) Bilateral optic neuritis treated with fingolimod (a sphingosine-1-phosphate–receptor modulator) in a woman with multiple sclerosis

iii) Unusual pale elevated lesion with pigment speckling but a depigmented halo, possibly 'unifocal helioid choroiditis', in a ~55-year-old woman

iv) Chronic relapsing inflammatory optic neuritis in a woman in her mid-20s

v) Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) in a 24-year-old woman

vi) Occipital metastatic breast cancer presenting with unusual floaters and blurred vision in 60-year-old woman

vii) Cutaneous melanoma metastatic to retina and vitreous presenting as vitreous floaters in a 67-year-old man

viii) 'Massive deposition of soft fluid-type drusen complicated by PEDs and new vessels' in a 43-year Māori woman

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