

## Age-related Macular Degeneration – An Asian Perspective

Tock-Han Lim,<sup>1,2</sup>*MMed, FAMS, FRCSEd*, Augustinus Laude,<sup>1,2</sup>*MBChB, MRCSEd (Ophth), MMed*

### Abstract

**Introduction:** Age-related macular degeneration (AMD) is the top blinding condition in developed countries. Dry AMD progresses slowly. Patients with dry AMD usually retain good vision until geographic atrophy or wet transformation sets in. Wet AMD causes rapid visual loss through chronic progressive or recurrent leakage and haemorrhage. Fundus biomicroscopy provides the clinical diagnosis, confirmed with fundus fluorescein angiogram (FFA). FFA also provides qualitative information on the rate of leakage. However, it does not adequately delineate the offending vascular lesion except in pure classic choroidal neovascularisation (CNV). Advancement in imaging technology employing confocal scanning laser ophthalmoscope indocyanine-green angiography (CSLO-ICGA) allows for accurate identification and delineation of the offending vascular lesion in 95% of cases, and for vascular subtyping into CNV, polypoidal choroidal vasculopathy (PCV) and retinal angiomatous proliferation (RAP). These vascular subtypes have different natural histories, and may respond differently to standard therapies. **Methods:** In a case series of 158 Asian eyes with wet AMD in Singapore, CNV was found in 85%, PCV in 34% and RAP in 5%. The relative proportion is different from published data involving Caucasian patients. Evidence-based treatment of extrafoveal classic CNV is thermal laser photocoagulation. Evidence-based treatment of subfoveal CNV includes periodic intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents such as ranibizumab or pegatanib, and photodynamic therapy (PDT) with verteporfin for suitable lesions. Due to cost considerations, off-label intravitreal injection of bevacizumab, an agent approved for metastatic colorectal cancer, may be considered on a compassionate-use basis. Other treatment modalities include direct thermal photocoagulation of extrafoveal PCV and CSLO-ICGA-guided PDT for occult CNV and PCV. Extrafoveal Stage-1 RAP can be treated with thermal laser photocoagulation. As wet AMD is a chronic recurrent condition, monitoring for treatment response and recurrence is of utmost importance. Optical coherence tomography provides objective measurement of the retinal thickness. Together with serial fundus photographs, it is invaluable for disease monitoring. With optimal treatment, avoidance of moderate visual loss over 24 months can be achieved in over 90% of cases, and a significant visual improvement of 3 lines (LogMAR) can be expected in about a third of cases. **Conclusion:** Optimal management using new pharmaco-therapies is unfortunately very costly at this juncture, and beyond the means of many Asian patients. Research into alternative cost-effective treatments is urgently needed.

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### Introduction

Age-related macular degeneration (AMD) is a group of non-Mendelian disorders which share the common manifestation of chronic progressive degeneration of the macula involving changes in the neuro-sensory retina, retinal pigment epithelium (RPE) and/or the inner choroid in patients above 50 years of age.

AMD is the commonest cause of irreversible blindness in developed countries. With a rapidly ageing population in

Singapore and other newly industrialised Asian countries, AMD is expected to be one of the top blinding conditions in this region.

### Classification

AMD is generally classified into dry and wet forms. While the majority of patients with AMD have the dry form, the more serious and rapidly progressive wet form accounts for 80% of blindness among AMD patients.

<sup>1</sup> The Eye Institute, National Healthcare Group, Singapore

<sup>2</sup> Department of Ophthalmology, Tan Tock Seng Hospital, Singapore

Address for Correspondence: A/Prof Lim Tock Han, The Eye Institute, National Healthcare Group c/o CSO5B, Tan Tock Seng Hospital, Jalan Tan Tock Seng, Singapore 308433.

Email: Tock\_Han\_Lim@nhg.com.sg

### **Dry Age-related Macular Degeneration**

The dry form of AMD is characterised by the presence of (1) drusen, (2) RPE atrophy and/or (3) pigmentary disturbance, in the absence of exudative changes (see below). When a large confluent area of RPE atrophy occurs, it is known as geographical atrophy (GA). Clinical impression among Asian ophthalmologists suggests that GA is less common among Asians than among Caucasians.

Each druse can be classified (1) by its size into small, medium or large, (2) by its border appearance into soft or hard, or (3) by the distribution into confluent or discrete. Soft confluent large drusen with pigmentary disturbances confer the highest risk of transformation into wet AMD.

Dry AMD is usually associated with a very mild and very slow decrease in visual acuity, usually not worse than 6/12. Most patients are asymptomatic. However, GA is associated with significant central visual loss; hence, it is classified together with wet AMD as “advanced AMD”.

Dry AMD is a clinical diagnosis. Investigations are usually unnecessary. In cases where fundus findings are equivocal for wet manifestations, optical coherence tomography is useful to detect subtle retinal thickening and/or sub-retinal fluid.

In dry AMD, fundus fluorescein angiogram (FFA) would show hyperfluorescence due to transmission defects and staining of drusen without leakage. Indocyanine-green (ICG) angiogram shows areas of clearer view of large choroidal vessels due to the loss of RPE and choriocapillaries. Occasionally, “dormant” or “mature” choroidal neovascular network (CNV) and/or polypoidal lesions can be detected in the angiograms of patients with dry AMD.

### **Wet Transformation**

Smoking increases the risk of wet transformation and visual loss 3 to 5 fold.<sup>1</sup> Cessation of smoking reduces this risk by years. However, most members of the public do not associate smoking with blindness.<sup>2</sup> Many would consider stopping smoking if they had known that smoking increases the risk of blindness. Public education is needed to bridge this gap of knowledge among smokers.

The Age-related Eye Disease Study (AREDS)<sup>3</sup> has shown that dry AMD patients with significant changes (Category 3 and 4) benefit from high dose vitamin A, C, E and zinc supplements, with 19% risk reduction of moderate visual loss, and 25% risk reduction of progression to advanced AMD over 5 years. As the macular changes of AREDS Category 3 and 4 AMD can be detected by standard non-mydratric fundus photography, it opens up the possibility of screening, early detection and preventive treatment for the population at risk (age above 50).

Early detection of wet transformation is crucial for early

treatment. Traditionally, patients are taught home self-monitoring using the Amsler grid. The preferential hyperacuity test has been shown to be more sensitive than the Amsler grid for the detection of wet transformation.<sup>4</sup> The patient may present with a sub-acute drop in vision and/or metamorphopsia.

Wet transformation can be confirmed with careful fundus slit-lamp bio-microscopic examination (looking for features of leakage and bleeding), optical coherence tomography (OCT) (to detect retinal thickening) and FFA (to look for fluorescein leakage).

### **Exudative or Wet Age-related Macular Degeneration**

Wet AMD occurs when abnormal vascular lesions form or proliferate deep into the Bruch’s membrane. It is suggested that these lesions form due to the ischaemia of the inner choroid. Together with other unknown triggers, the inflammatory cascade is activated. Inflammatory cytokines and vascular endothelial growth factors (VEGFs) are up-regulated, leading to the formation of abnormal vascular lesions. These leaks and/or bleed lead to further damage of the RPE and the associated photoreceptors.

The most important form of vascular lesion of wet AMD is CNV. CNV forms when new endothelial channels sprout from the inner choroid, breach the anatomical barrier of Bruch’s membrane and proliferate in the sub-RPE space forming Type 1 CNV. It may further breach the RPE and occupy the sub-retinal space forming Type 2 CNV. Note that Types 1 and 2 CNV are best understood as histopathological terms.

Wet AMD is characterised by exudative and/or haemorrhagic changes in the macula, manifesting as retinal thickening, sub-retinal fluid accumulation, intra- or sub-retinal exudates, intra- or sub-retinal haemorrhage, RPE detachment and/or sub-RPE haemorrhage. It is a clinical diagnosis supported by characteristic FFA findings.

### **Fundus Fluorescein Angiography**

In wet AMD, FFA shows features of leakage (increasing hyperfluorescence with blurring of margin), pooling from serous pigment epithelial detachment (PED) and blocked fluorescein from haemorrhage. These are the results of the vascular lesions of AMD but not the lesions themselves. For example, a zone of undulating punctate fluorescein staining depicts an area of RPE damage and detachment (fibrovascular PED), suggesting the presence of occult CNV beneath. An area of pooling with a notch depicts a serous PED possibly caused by an occult CNV at its notch (also termed as vascularised PED). An area of variegated staining with jagged margins depicts disciform scar formation. None of these FFA features show the offending vascular lesion itself; hence, the term occult CNV is a FFA

term. Occult CNV accounts for about 88% of cases with wet AMD in the Western population. To add to the confusion, FFA pattern of undulating punctuate hyperfluorescence (depicting fibrovascular PED) is also termed as Type 1 occult CNV; whereas FFA showing late leakage of unknown origin (mainly vascularised PED and disciform scars) is termed Type 2 occult CNV. These are FFA terms not to be confused with Types 1 and 2 CNV (see above), and are best avoided.

In about 12% of wet AMD, however, the offending CNV can be imaged by FFA. It shows up in the earliest phases of FFA as a well-defined hyperfluorescent lacy pattern that quickly leaks and smudges its own outline. The FFA term for this lesion is “classic CNV”. It is likely that classic CNV represents mainly Type 2 CNV, and possibly Type 1 CNV with significant overlying RPE atrophy, hence the ability to image it clearly in FFA.

Reading the FFA, if any part of the lesion lies under the centre of the foveal avascular zone (FAZ), it is termed as subfoveal CNV. If the lesion encroaches to 1-199 microns of the FAZ, taken to be twice the width of the retinal artery crossing the optic disc margin, it is termed as juxtafoveal CNV. If the lesion is 200 microns or further beyond the FAZ centre, it is extrafoveal. Notice that localisation is only accurate for classic CNV where its outline is reasonably clearly demarcated by FFA.

As for occult CNV, the actual extent of the vascular lesion is often unknown if it is based on reading the FFA alone. The reason is that sodium fluorescein is only about 80% protein-bound. It rapidly extravasates from the CNV and enters the interstitial spaces, from which it enters and stains the RPE cells. Light emitting from sodium fluorescein is green and easily absorbed by haemoglobin of the overlying haemorrhage. To compensate for its inaccuracy, the FFA extent of occult CNV is taken to be the whole contiguous area inclusive of stippled hyper-fluorescence, pooling and blocked fluorescence, often over-estimating the actual size of the occult CNV.

### **Indocyanine-green Fundus Angiography**

To image the actual offending vascular lesions better, ICG has been used. ICG angiography was largely adapted from the cardiologists, who use it to evaluate cardiac output. It is 98% protein bound and therefore stays within the vascular lumen long enough for its concentration to be built up sufficiently to be imaged. It emits infrared light that passes through haemorrhage much better than the green light from sodium fluorescein. With ICG angiography, it is possible to image the choroidal vasculature through intact RPE, which imbibes ICG much later than sodium fluorescein.

The early ICG fundus angiograms were performed by

light flashes and recorded on infrared film. With the advent of infrared charged-couple device sensors, the age of digital flash-ICG angiogram (F-ICGA) arrived. Early F-ICGA suffered from poor image quality such that CNV cannot be accurately imaged. However, F-ICGA was able to delineate focal, nodular hyperfluorescent lesions previously not observed. These were initially termed “focal CNV”, an F-ICGA term, denoting small areas of focal ICG hyperfluorescence less than 1 disc diameter in size. Similarly, patches of ICG hyperfluorescence that were larger than 1 disc-diameter were termed “plaque CNV”, another F-ICGA term. There is now reason to believe that many cases of focal CNV were in fact polypoidal choroidal vasculopathy (PCV) or retinal angiomatous proliferation (RAP), instead of CNV. Similarly, some cases of plaque CNV, which show up best in the late phase of F-ICGA, are likely to depict late accumulation of ICG in patches of damaged RPE, instead of CNV.

### **Polypoidal Choroidal Vasculopathy**

As F-ICGA improves, many cases of focal CNV were noted to show nodular hyperfluorescence in clusters (appearing as a bunch of grapes) or arranged in rings or wreath formations. These lesions were noted to be associated with clinical presentations that were slightly different – the patient tends to present acutely with recurrent episodic submacular and sub-RPE haemorrhage, although many present with chronic progressive submacular exudation similar to the usual cases of wet AMD. Severe bleeding from PCV can result in breakthrough vitreous haemorrhage and even spontaneous suprachoroidal haemorrhage.<sup>5</sup> These lesions were termed PCV, an ICG diagnosis. As there are important differences from the usual cases of wet AMD, PCV was thought to be a different disease altogether. The age of onset is younger, it occurs more often in Asians and there is a notable absence of drusen, the hallmark lesion of AMD. The visual prognosis is surprisingly better, given the haemorrhagic presentation, with long symptom-free periods between each bleeding episode. However, about half of these cases progress with a relentlessly recurrent or chronic downhill course, not unlike wet AMD.

### **Confocal Scanning Laser Ophthalmoscopy – ICG Angiography**

With the advent of confocal technology, scanning laser ophthalmoscopy and high speed digital infrared sensors, the image quality of the ICG angiogram has improved so much that the earliest phase of the ICG angiogram can be captured in dynamic image sequences. Known as confocal scanning laser ophthalmoscopy ICG angiography (CSLO-ICGA), the offending vascular lesions can be imaged in the first 30 seconds of ICG dye transit through the choroidal vasculature. Dynamic digital image sequence allows the

observer to play the sequence back and forth watching the lesion fill, before the dye leaks into the interstitium and stains the RPE along with the tissue spaces.

In an unpublished review of 158 eyes of 156 patients with fundus and FFA features of wet AMD imaged with CSLO-ICGA in a tertiary AMD referral centre in Singapore, the offending vascular lesion can be imaged in 150 (95%) eyes. Of these, 85% had CNV, 34% had PCV and 5% had RAP. About 27% had more than one vascular subtype at some point in the follow-up period.<sup>6</sup> Note that the terms CNV, PCV and RAP were used according to CSLO-ICGA definitions. In particular, the vascular networks of CNVs were actually imaged, often complete with the feeder vessel(s) and drainage vein(s) before it was called CNV in CSLO-ICGA terminology. Five per cent had classic CNV, with well-defined lacy vascular network imaged in the early sequences of CSLO-FFA, as well as CSLO-ICGA (Fig. 1), while 80% had occult CNV, which were only imaged in CSLO-ICGA but not in CSLO-FFA.

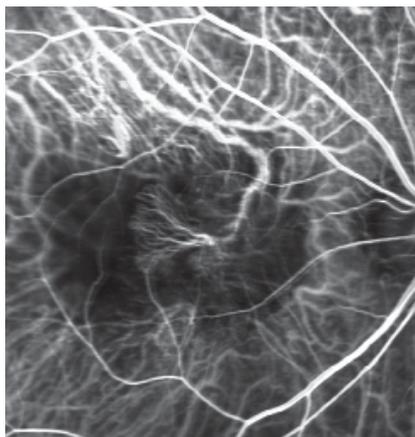


Fig. 1. CSLO-ICGA image of a choroidal neovascularisation lesion.

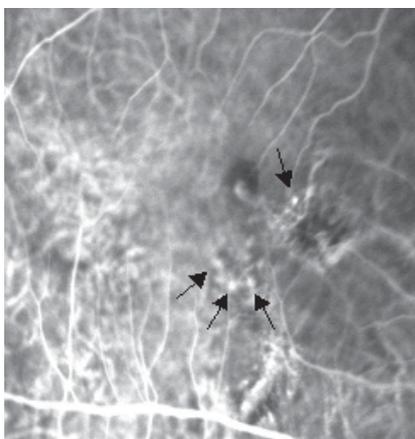


Fig. 2. CSLO-ICGA image of polypoidal choroidal vasculopathy (arrows).

PCV lesions are better imaged using CSLO-ICGA compared to F-ICGA (Fig. 2), often showing clearly the branching vascular network (BVN) vessels that feed into these hyperfluorescent polyps. Some of these BVN vessels appear to start from a single feeder vessel, or from a discrete vascular in-growth site, indistinguishable from a CNV complex, as these lesions are assumed to have punched through the Bruch's membrane to occupy the sub-RPE location. In other cases, ICG dye appears in these BVN vessels almost simultaneously, as if the lesions were telangiectasia of the choriocapillaries, possibly locating within the inner choroid. Some BVN leaks together with the polyps, and continue to leak after the polyps were focally ablated, behaving exactly like CNV. Some cases present initially with CNV but sprout polypoidal lesions on follow-up. Some present with CNV in one eye but PCV in the other. It has been shown that VEGF is also elevated in patients with PCV, but at a lower level compared to CNV. As such, some cases of PCV may represent a vascular response to an intermediate level of VEGF of wet AMD.

### Retinal Angiomatous Proliferation

RAP, on the other hand, usually follows an aggressive, recalcitrant downhill course. It differs from the other vascular subtypes in that the vascular lesion starts in the inner retina. Tiny intra-retinal vascular anastomosis occurs between the terminal branches of retinal arteries and veins, occurring commonly near the edge of FAZ (Stage 1). The vascular lesion grows downwards and proliferates in the sub-retinal space (Stage 2). Further downward growth sees the lesion penetrate the RPE and proliferate in the sub-RPE space simulating a CNV (Stage 3).

Early stages of RAP typically present with tiny intra-retinal haemorrhages, blunt-ending vessel(s) near the edge of FAZ, typically occurring over a serous PED. FFA typically shows minimally classic occult CNV, with focal

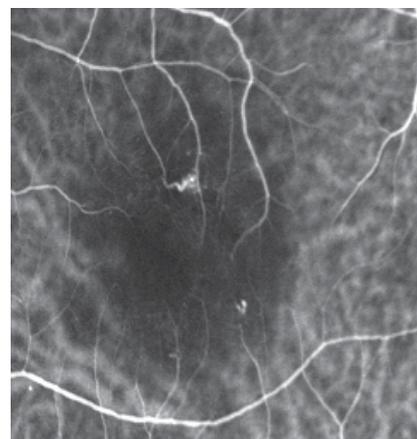


Fig. 3. CSLO-ICGA image of a retinal angiomatous proliferation lesion.

hyperfluorescence(s) near the FAZ edge. F-ICGA reveals one or more “nodular hyperfluorescence” near FAZ. It may be misdiagnosed as PCV. CSLO-ICGA is the key to the diagnosis of RAP – retinal arterial filling and venous drainage of the RAP lesion can be followed during the AV transit phase (Fig. 3). “CNV” that fluoresce after, instead of before, retinal artery filling should raise the suspicion of RAP.

OCT of the macula is an important tool in the management of wet AMD. Serial OCTs provide quantitative assessment of the treatment response, and a means to detecting early recurrence.

### Treatment Options for Wet AMD

Evidence-based treatment of wet AMD has been guided by 3 groups of well designed randomised controlled trials.

The Macular Photocoagulation Study (MPS) has shown the treatment benefits of thermal photocoagulative ablation for extrafoveal<sup>7</sup> and juxtafoveal<sup>8</sup> classic CNV. Till today, it remains the treatment of choice for extrafoveal (and perhaps, juxtafoveal) classic CNV. For juxtafoveal classic CNV where laser photocoagulation is deemed risky in consideration of laser scar expansion, other treatment options are now available. Even with successful treatment, recurrence is common.

As for occult CNV that is located well clear of the FAZ centre, it is reasonable to offer thermal laser photocoagulative ablation, inferring from the results of MPS. In this aspect, CSLO-ICGA offers much better delineation and localisation of the CNV complex than FFA. In fact, occult CNV may be deemed subfoveal on FFA, but clearly extrafoveal on CSLO-ICGA. In such instances, CSLO-ICGA-guided thermal laser photocoagulation for extrafoveal CNV may be a reasonable treatment option.

At the turn of the millennium, treatment of wet AMD has been largely dominated by photodynamic therapy (PDT), considered a new paradigm then. A photo-sensitising agent verteporfin is first infused intravenously, and become concentrated in the neovascular complex through its binding to LDL receptors. Verteporfin is then activated by a 689nm laser targeted over the area of CNV leading to the release of free oxygen radicals, damaging the endothelial cells and leading to intraluminal platelet aggregation and thrombosis.

The Treatment of AMD by Photodynamic Therapy (TAP) Study<sup>9</sup> showed treatment benefits of PDT in predominantly classic CNV (CNV with more than 50% classic component based on FFA). The Verteporfin In Photodynamic Therapy (VIP) Study<sup>10</sup> showed treatment benefits for pure occult lesion that are either small (<4 disc areas) or with poor vision (worse than 20/50). Post-hoc analysis of TAP and VIP data also suggests that treatment outcome is associated more with the size of the lesion than the lesion component.<sup>11</sup>

It is also suggested that treatment may be beneficial for minimally classic and pure occult lesions 4 disc-area or smaller in size. The treatment benefits of PDT, however, are modest. Overall, about 2/3 of the treated group compared to 1/3 of the placebo group avoided moderate visual loss (MVL) defined as a loss of 15 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters over 1 year. Few of the treated patients experienced significant visual gain of 15 ETDRS letters or more.

Unfortunately, both TAP and VIP trials were based on FFA, both in the definition of lesion component and in the planning of the treatment zone. As such it is unclear if the TAP and VIP studies included cases of PCV and/or RAP. In addition, FFA guidance in treatment zone planning for occult lesion is often highly subjective and unsatisfactory. Although CSLO-ICGA is able to better elucidate the vascular lesion (and therefore offer better targeting), CSLO-ICGA-guided PDT is considered empirical because the major PDT trials that have been reported were FFA based. In our centre, a retrospective review of CSLO-ICGA-guided PDT for CNV could achieve avoidance of MVL in 76% of cases at 12 months.<sup>12</sup>

Meanwhile, the TTT4CNV trial<sup>13</sup> has not shown the treatment benefits from trans-pupillary thermal therapy (TTT) that many prior interventional case series seemed to suggest. Intravitreal triamcinolone acetonide (IVTA) injections had initially shown benefits with reduction of OCT thickness in most case series, but benefits in visual acuity are less clear. Significant elevation of intraocular pressures was noted in a significant proportion of patients, some requiring surgical drainage procedures. Currently, with the wide use of intravitreal anti-VEGF treatment, there has been a corresponding reduction in interest in IVTA for wet AMD.

### Anti-VEGF Therapy

Pegatanib (Macugen, OSI Pharmaceuticals Inc, USA) was the first intraocular anti-VEGF agent that was FDA approved for the treatment of wet AMD. It is a RNA aptamer that binds to VEGF isoform 165. VEGF Inhibition Study in Ocular Neovascularization (VISION) Trial<sup>14</sup> showed that 6 weekly intravitreal injections of Macugen achieved avoidance of MVL in 70% of patients at week 54 for the 0.3 mg group. However, the endophthalmitis risk was significant, at 1.3% per patient per year.

It was ranibizumab (Lucentis, Genentech Inc, USA), a humanised, monoclonal, anti-VEGF antibody Fab fragment, which heralded in the current paradigm of wet AMD therapy. In the Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular AMD (MARINA) Trial,<sup>15</sup> monthly intravitreal injections of Lucentis in cases not eligible for PDT (e.g.

minimally classic occult CNV) achieved over 95% of avoidance of MVL at 12 months. This was the best result achieved for any wet AMD therapy. The results were maintained at 24 months. In fact about 34% of patients in the treated arm enjoyed 3 or more ETDRS lines of improvement in visual acuity. In the ANTi-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularization in AMD (ANCHOR) Trial,<sup>16</sup> a head to head comparison with PDT for predominantly classic CNV, Lucentis was again shown to achieve similar results, significantly better than PDT at 12 months. The FOCUS Study<sup>17</sup> compared PDT with combined PDT and Lucentis and showed that while patients treated with a combination regimen did far better than with PDT alone, the results were similar to Lucentis alone in the MARINA and ANCHOR trials, suggesting that the initial PDT may not add much to the efficacy of monthly Lucentis injections alone.

Hence, for the first time, a wet AMD therapy was shown to improve rather than to maintain vision. However, these excellent results came at a cost. Not only was the cost prohibitive for most patients, but the cumulative endophthalmitis rate was also about 1.4% in 24 injections over 24 months. The PIER<sup>18</sup> trial (a Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration) was convened to see if a reduced frequency beyond the first 3 monthly injections could reproduce the excellent results. Unfortunately, reducing the injection frequency to 3 monthly after the initial 3 injections could not reproduce the same excellent results.

As it stands today, the most effective evidence-based therapy for any FFA lesion subtype of wet AMD is monthly injections of Lucentis for up to 24 months. The cost of Lucentis injections currently stands at about US\$14,000 per year, which is beyond the means of most patients in Singapore.

Serious financial constraints faced by patients and ophthalmologists have led to the widespread use of off-label intravitreal bevacizumab (Avastin, Genentech Inc, USA) as a low-cost substitute for ranibizumab. Bevacizumab, a systemic anti-VEGF agent, is a “cousin molecule of ranibizumab”, having similar binding sites for VEGF. It has been approved by the FDA for the treatment of metastatic colorectal carcinoma. Off-label use of intravitreal Avastin has been widely applied on a compassionate basis. There have been several published interventional case series suggesting that it is efficacious.<sup>19-21</sup> These are largely open-labelled non-comparative studies with short follow-up periods. Several studies in both animal and human eyes suggest it is safe at the dose of 1 to 2.5 mg per intravitreal

injection.<sup>22-24</sup> The optimal injection regimen is unknown. Many ophthalmologists adopt a strategy of “monthly injection till quiescence” and “re-injection at recurrence”. Whether monthly repeated intravitreal injections of Avastin are associated with the same thromboembolic risks of systemic intravenous infusions for the oncology patient is currently unknown.

All 3 widely used anti-VEGF therapies require multiple periodic intravitreal injections, which expose patients to a small but significant cumulative risk of endophthalmitis. To reduce the re-injection frequency, some AMD experts advocate the use of combined angio-occlusive therapy (verteprofin PDT mainly) and angiostatic therapy (anti-VEGF and/or intraocular steroid).<sup>25,26</sup> Encouraging results were obtained by combining PDT with intravitreal Avastin and intravitreal dexamethasone injections.<sup>27</sup>

In addition, most pharmacotherapy trials have been FFA based. Therefore, cases with PCV and RAP were likely to be included in the study cohort. PCV, in particular, represents about 1/3 of cases with wet AMD in Singapore. Unlike CNV, the treatment of PCV has not been clearly defined through well-designed randomised controlled trials. However, preliminary data from The Eye Institute (TEI), National Healthcare Group, Singapore suggests that the condition responds well to CSLO-ICGA-guided thermal laser photocoagulation of extrafoveal polyps, achieving avoidance of MVL in 93% of patients, and visual improvement of 3 ETDRS lines or more in about 46% of patients at 12 months.<sup>28</sup> For subfoveal or juxtafoveal polyps, PDT may be applied. Similarly, for PCV lesions where the branching vascular networks (or CNV) were leaking, PDT may be the preferred treatment. Preliminary results from TEI and published data elsewhere showed avoidance of moderate visual loss in 77% to 90% of patients at 12 months.<sup>29,30</sup>

### Other Treatment Modalities

Other than pharmacotherapies, surgical options such as macular translocation with 360 retinectomy or with punctuate retinotomy may still be offered in very specialised surgical retinal centres. Surgical risks such as proliferative vitreoretinopathy will continue to limit their acceptance. Similarly, submacular surgery involving removal of Type 2 CNV may achieve good results in specialised surgical retinal centres.<sup>31</sup> However, case selection is crucial to achieving good results (Type 2 CNV, with vascular ingrowth site distant from fovea). Choroid, RPE cell and retinal stem cell transplantations are currently undergoing development and evaluation. Several new pharmaco-therapies are also currently undergoing investigations, including VEGF Traps, Small Interfering RNA (siRNA) and Tyrosine Kinase Inhibitor.

## Visual Rehabilitation

Visual rehabilitation of wet AMD patients is often under-emphasised. Reading aids, distant visual aids, motility aids, home environment re-design and guide dogs can go a long way to improve the quality of the lives of AMD patients. Intraocular retinal prosthesis may offer hope in the future to restore central vision lost to AMD.

In response to the emerging challenges posed by AMD on the population in Singapore, we are also seeing increased international collaboration in the Asia Pacific region. One such example would be the setting up of an Asia Pacific office for the AMD Alliance International, a non-profit coalition of vision, research and seniors' organisations working to combat blindness from AMD, with the aims of raising awareness of AMD, its treatment and rehabilitation options and the importance of early detection.<sup>32</sup>

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