Optimising the management of choroidal neovascularisation in Asian patients: consensus on treatment recommendations for anti-VEGF therapy

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ABSTRACT

In Asian countries, age-related macular degeneration (AMD), specifically wet AMD or choroidal neovascularisation (CNV), is an important cause of blindness and visual handicap. Vascular endothelial growth factors (VEGF) play an integral role in the development of CNV and thus provide an important therapeutic target. Current treatment paradigms for neovascular AMD recognise the place of photodynamic therapy (PDT) in the management of this condition. However, combination therapy targeting different pathways to produce a synergistic effect may result in improved visual outcomes and reduced duration of treatment. Anti-VEGF therapy has greatly improved treatment outcomes in patients with CNV, and a growing body of evidence supports the role of these agents as monotherapy or in combination with PDT. In particular, anti-VEGF may be a first-line treatment option in certain types of subfoveal myopic CNV as well as for classic and occult juxtafoveal and subfoveal CNV. The implementation of evidence-based medicine into current clinical practice is paramount to improving patient care. The authors, who are also members of the Singapore Medical Retina Advisory Board, outline the consensus points and recommended treatment algorithms based on currently available knowledge to provide a structured management approach to the treatment of Asian patients with CNV.

Keywords: age-related macular degeneration, choroidal neovascularisation, monoclonal antibody, ranibizumab

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INTRODUCTION

Age-related macular degeneration (AMD) is an important cause of blindness and visual handicap in Asian countries with an ageing population. Although wet AMD or choroidal neovascularisation (CNV) constitutes only 18% of AMD, it is a major cause of blindness (90%).[1,2] Polypoidal choroidal vasculopathy (PCV) may constitute as much as 50% of cases of wet AMD in some Asian countries. CNV occurs when the integrity of Bruch's membrane is disrupted and neovascular complexes from the choroid grow into the subpigment epithelial and subretinal spaces. CNV is characterised by neovascularisation from the choroidal blood vessels through Bruch's membrane into the sub-retinal pigmented epithelial (RPE) space or the subretinal space.[1,3] Pigment epithelial detachment (PED) occurs if fluid, blood, CNV and/or drusen accumulate beneath the RPE, leading to a separation of the retinal pigment epithelium from Bruch's membrane. On the basis of its appearance on fluorescein angiography, CNV can be classified as classic, occult or mixed.[1] CNV secondary to pathological myopia is relatively common in Asian populations, with the prevalence rates ranging from 9% to 21%.[4] In contrast to CNV secondary to AMD, which usually occurs in the sub-RPE space, myopic CNV is mainly subfoveal or juxtafoveal with minimal subretinal fluid or exudate.[4]

There is low awareness of AMD among the Asia-Pacific population. There are also few well-conducted population-based studies on the prevalence of this disease.[2,5] In the AMD 2005 Global Report, which surveyed more than 15,000 people in 14 countries, Asian countries had the lowest awareness of AMD compared with other countries.[6] A random telephone survey (n = 520) conducted in Singapore revealed that only 7.3% of residents were aware of AMD, which is comparable to that observed in Hong Kong, Japan, Spain, Italy and the Netherlands (less than 10%).[7] In the United States, Australia and Canada, awareness of AMD ranges from 21% to 30%,[6] whereas in the United Kingdom, South Africa, Germany, France, Ireland and Switzerland, it is between 10% and 16%.

In this article, the authors, who are also members of the Singapore Medical Retina Advisory Board, focus

on the role of anti-vascular endothelial growth factors (VEGFs) in AMD and the potential of anti-VEGF-based combination therapy in the treatment of CNV and/or PCV. We also present a number of consensus points and treatment algorithms for the management of Asian patients with these conditions.

ANTI-VEGFS FOR AMD CNV

VEGF plays a very important role in the development of CNV. VEGF is secreted by hypoxic RPE cells and induces endothelial cell proliferation and retinal vascular permeability. It has been identified as a major mediator of retinal ischaemia-associated neovascularisation.[8] The advent of anti-VEGFs has vastly improved treatment outcomes in patients with CNV, in a manner that is unprecedented by conventional treatments such as laser photocoagulation and photodynamic therapy (PDT). While vision loss is inevitable even with conventional treatments, anti-VEGFs are able to improve or maintain vision in the majority of patients.

Current data indicate that clinical response to anti-VEGFs needs to be individually assessed and cannot be estimated based on the onset or duration of action. Ranibizumab, a humanised monoclonal antibody that inhibits all subtypes of VEGF-A, has a rapid onset of action. Optical coherence tomography (OCT) changes can be observed as early as 12 hours to 24 hours post ranibizumab injection.[9] Bevacizumab is a humanised monoclonal antibody that also binds all VEGF subtypes, but has a lower affinity and longer onset of action than ranibizumab,[10] usually 3–4 days, with visual improvements reported within a week. While ranibizumab gained FDA approval for the treatment of neovascular AMD in 2006, intravenous bevacizumab was approved for use in metastatic colorectal cancer in 2004, and off-label use of intravitreal bevacizumab in AMD is practised worldwide.[10]

A recent study that examined the factors influencing treatment and re-treatment decisions by retina physicians showed that physicians are universally switching to the pan-VEGF blocking agents, ranibizumab and bevacizumab, on a *pro re nata* (prn) dosing schedule because neither patients nor physicians want monthly injections.[11] This study also determined that if monthly injections are not administered, a combination of clinical examination and qualitative OCT can be used to guide anti-VEGF treatment by maintaining 'normal' retinal anatomy in an attempt to maximise the benefit (visual acuity [VA] gains) to risk (number of injections required) ratio.[11] Good VA outcomes, similar to those reported in phase III clinical trials, can be achieved with a mean of 9.9 ranibizumab injections over a 24-month period, according to the results of the Prospective OCT Imaging of Patients with Neovascular AMD Treated with intraOcular Ranibizumab (PrONTO) study.[12] Ideally, patients should be reviewed monthly to assess whether repeat anti-VEGF injections should be given.

Clinical Efficacy

The efficacy of anti-VEGF agents has been demonstrated in subfoveal CNV secondary to AMD of all angiographic subtypes, whether classic or occult. This efficacy was independent of PDT.[13] Anti-VEGF treatment with ranibizumab resulted in sustained visual improvement and prevented progression to 20/200 in the multicentre, two-year Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular AMD (MARINA; n = 716) study. After 24 months, over 90% of patients lost fewer than 15 letters (from baseline VA) following monthly intravitreal ranibizumab (0.3 mg or 0.5 mg) vs. 53% in the sham arm.[14] Furthermore, ranibizumab 0.3 mg and 0.5 mg improved the mean VA to 6.5 and 7.2 letters, respectively, while the sham arm lost 10.4 letters ($p < 0.001$). In patients with primary or recurrent disease, ranibizumab was shown to be more effective than verteporfin PDT in the multicentre, two-year ANti-VEGF Antibody for Treatment of Predominantly Classic CHORoidal Neovascularisation in AMD (ANCHOR; n = 423) study.[15] The majority (68%) of verteporfin PDT-treated patients progressed to VA 20/200 or worse, compared with 22.9% and 20.0% of patients treated with ranibizumab 0.3 mg and 0.5 mg, respectively. In the recent 24-month subgroup analyses of MARINA and ANCHOR, ranibizumab was found to be beneficial for all CNV subtypes.[16] Initial VA, lesion size and age were the most important predictors of VA outcome.

Evidence from a multicentre, retrospective case series in patients with subfoveal CNV secondary to AMD (n = 63) demonstrated the beneficial effect of bevacizumab (1.25 mg or 2.5 mg) in stabilising or improving VA, although these improvements only reached statistical significance for early lesions ($p \leq 0.03$).[17] Improvements in VA were evident as early as one week after intravitreal bevacizumab 1.25 mg, and these effects were accompanied by improvements in macular thickness in a small six-month pilot study (n = 26).[18]

RPE tears or rips are increasingly reported with intravitreal injection of anti-VEGFs.[19-26] A number of large retrospective case series have reported that RPE rips occur with an incidence of 0.6%–2.2% within four days to 16 weeks of anti-VEGF injection.[21,22,24] Data

from the largest series (n = 2,785 intravitreal injections of bevacizumab) indicated that vascularised PED was present in the majority (95%) of cases. These data indicate that large PED size is a predictor of RPE tears, and a small CNV size to PED size (< 50%) is more common in eyes with RPE tears.[21] An interventional case series reported fibrovascular retinal PED in 5% of patients (n = 164 eyes) receiving ranibizumab; the authors concluded that RPE rips occur with a low incidence and may be due to patient-related factors rather than treatment effect.[25]

Table I. Effects of upregulation of VEGF in the retina post PDT.[13]

Negative effects	Recurrent growth CNV Increased permeability and leakage from CNV
Positive effects	Prevent hypoxia-induced retinal damage Allow surrounding choroidal vessel recovery Encourage maturation of CNV that is: - less permeable - less susceptible to re-initiate NV

VEGF: vascular endothelial growth factors; PDT: photodynamic therapy; CNV: choroidal neovascularisation; NV: neovascularisation

Ocular safety

Given that bevacizumab is not approved in AMD/CNV, most of the ocular safety data pertains to ranibizumab. Serious ocular adverse events following 24 months of treatment with ranibizumab 0.3 mg or 0.5 mg were uncommon in both the MARINA and ANCHOR studies.[14,15] Endophthalmitis occurred with an incidence of 0.8%–1.4%[14,15] and rates of severe intraocular inflammation were 8%–15%, with most inflammation classified as trace or 1+.[14,15] Ranibizumab had no long-term effects on intraocular pressure over the two-year follow-up.[14]

Systemic safety of anti-VEGF agents

To date, there is a lack of systemic safety data on anti-VEGF agents in CNV. The ongoing Comparison of AMD Treatments Trials (clinicaltrials.gov/ct2/show/NCT00593450) aims to compare the relative efficacy and safety of ranibizumab and bevacizumab in patients aged ≥ 50 years with active subfoveal CNV. This trial will yield safety data in this patient population.

COMBINATION THERAPY FOR AMD CNV

The availability of verteporfin PDT in the late 1990s led to a paradigm shift in the treatment of subfoveal CNV. While anti-VEGFs act via anti-angiogenesis, verteporfin PDT produces a photo-thrombotic reaction that results in angio-occlusion of the vessels; this action arrests CNV growth but does not obliterate the vessels. Due to its unique mode of action, the role of verteporfin PDT in the treatment of CNV cannot be undermined.

The visual outcomes of verteporfin PDT are influenced by three underlying mechanisms. Firstly, verteporfin PDT causes upregulation of VEGF in the retina, which leads to several negative (usually acute) and positive effects (Table I).[27] In particular, it causes the long-lasting effect of CNV maturation, which may have implications for the treatment of PCV. Secondly, PDT results in the release of a host of angiogenic factors, cytokines and vasoactive mediators that lead to an acute inflammatory response, which is usually self-limiting and dissipates within one month post-PDT. Thirdly, as opposed to upregulation of VEGF, verteporfin PDT downregulates pigment epithelium-derived factor, a potent angiogenic inhibitor that helps to reduce inflammation and vessel permeability.

It is therefore prudent to recognise the limitations of PDT treatment while attempting to maximise its strengths. Given the multifactorial nature of CNV, targeting different pathways may produce a synergistic effect, thereby improving visual outcomes. Combination therapy may improve VA, decrease the growth of CNV, reduce/prevent recannulisation and reduce the risk of visual disturbances while reducing the duration of treatment. The synergistic action of PDT (closure of CNV) and anti-VEGF/corticosteroid therapy (inhibition of angiogenesis and leakage) form the pharmacologic rationale for the combined use of these treatments in neovascular AMD.

Clinical efficacy

The phase I/II RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety trial comparing PDT with a combination of intravitreal ranibizumab and verteporfin therapy for subfoveal predominantly classic lesions secondary to AMD was the first study to demonstrate the efficacy of ranibizumab in this patient population.[28]

The multicentre, randomised MONT BLANC study is a 24-month study designed to demonstrate the non-inferiority of combined ranibizumab and verteporfin vs. ranibizumab monotherapy in patients with subfoveal choroidal neovascularisation secondary to AMD.[29] The results of the 12-month primary analysis confirmed the non-inferiority of combination therapy over ranibizumab monotherapy. At this time-point, mean visual acuity improved by 2.5 letters in the combination therapy group compared with 4.4 letters in those receiving ranibizumab alone. The proportion of patients who had a three-month treatment-free interval was 96% and 92% in the combination and monotherapy groups, respectively.[29] Thus, at the present time, there is no clear evidence to

Table II. Consensus recommendations for the treatment of CNV.

Non-AMD CNV	• Laser photocoagulation is recommended as first-line treatment for extrafoveal myopic CNV. • PDT is recommended as first-line treatment for juxtafoveal myopic CNV. • Under normal circumstances, PDT is the preferred treatment for subfoveal myopic CNV: - For small lesions, both PDT and anti-VEGF are effective. - In lesions with a large haemorrhage or coexisting cataract, first-line anti-VEGF may be preferable.
PCV	• In PCV with a polyp distant from the fovea and an inactive branching network, thermal laser ablation is recommended. • Depending upon the risk of laser scar expansion and patient factors, thermal laser ablation may be performed in juxtafoveal PCV. • For subfoveal or juxtafoveal polyps with dormant, non-leaking network vessels, PDT should be targeted at polyps only; anti-VEGF monotherapy is not recommended. • For juxtafoveal and subfoveal polyps that fail to close with initial treatment, repeat ICG and repeat treatment with ICG-guided PDT are recommended.
CNV	• Anti-VEGF may be administered for juxtafoveal and subfoveal CNV; lesion type should be determined first. • For extrafoveal CNV, where the lesions are clearly defined on ICG angiogram, thermal laser photocoagulation may be performed. • Juxtafoveal and subfoveal classic and occult CNV may be treated with monthly intravitreal anti-VEGF injections. • Where monthly injections are not practical, the PrONTO protocol of 3 loading doses, then 'as needed' with close monitoring.

CNV: choroidal neovascularisation; PCV: polypoidal choroidal vasculopathy; PDT: photodynamic therapy; VEGF: vascular endothelial growth factors; ICG: indocyanine green

support the use of combination therapy in patients with subfoveal choroidal neovascularisation secondary to AMD.

COMBINATION THERAPY FOR CONDITIONS OTHER THAN AMD CNV

Polypoidal choroidal vasculopathy

In addition to vascular polyps, the branching vascular network that supplies the polyps can become a major concern when making treatment decisions. While the branching vascular network may be dormant in some cases of PCV, it can be the main cause of leakage and exudation in other cases. The branching vascular network can continue to persist or even proliferate after thermal laser or PDT ablation of the polyps, causing new leakage. These 'feeder' vessels often behave like CNV.

For the treatment of PCV, the current data seems to suggest that anti-VEGF is ineffective in diminishing choroidal vascular polyps but may reduce exudation and macular thickening.[30] Therefore, a different strategy involving a combination of anti-VEGF treatment and angio-occlusive therapy using verteporfin PDT may need to be employed to target both the network vessels as well as the polyps. PDT is effective against primary PCV and is usually the preferred mode of treatment if active subfoveal or juxtafovel polyps are present, or if the polyps are not well visualised or the inter-connecting channels/ associated CNV become active. The use of PDT for PCV is supported by more than ten well-conducted interventional case series involving about 300 eyes, showing avoidance of moderate visual loss in 80%–100% of eyes that had received PDT for PCV.[31-40]

The rationale for the use of anti-VEGF treatment in PCV is based on the evidence that VEGF concentrations in aqueous humour are moderately increased in patients with PCV, although the levels are significantly lower than those in exudative AMD ($p = 0.045$).[41] Anti-VEGF agents improve VA (1.2 lines in three months) through the reduction of macular thickening, leakage, retinal oedema and sub-retinal fluid. However, they only have a partial effect on the regression of polyps.[30,42]

The combination of PDT and intravitreal triamcinolone acetate has been found to improve both visual function and indocyanine green angiogram (ICG-A) features in the short term, although the long-term outcome is complicated by cataracts.[32] It is therefore possible that combination therapy with PDT and anti-VEGF agents may be useful in certain cases of PCV.

CNV in pathological myopia

Patients with CNV secondary to pathological myopia have a poor long-term prognosis; approximately 90% have ≤ 20/200 vision after 5–10 years. In cases where there is angiographically proven myopic CNV, treatment should be considered. Following the Verteporfin in Photodynamic Therapy studies, which demonstrated the superiority of PDT over placebo for myopic CNV,[43] many interventional case series have since confirmed the benefits of PDT.[44-48]

Preliminary results on the use of anti-VEGFs for myopic CNV in Asian patients revealed that 90.9% of eyes treated had angiographic closure after three monthly injections, and 9.1% required further injections for up to six months.[49] Data from a small study (n = 8 eyes) in

Chinese patients with CNV secondary to pathologic myopia demonstrated that an intravitreal injection of bevacizumab (2.5 mg) significantly improved mean VA ($p = 0.017$) and reduced mean central retinal thickness ($p = 0.017$) after 12 months.[50] Larger studies are necessary to confirm these findings. A study comparing anti-VEGF alone with anti-VEGF and PDT demonstrated better visual results at 12 months with anti-VEGF monotherapy; 98.4% of patients lost < 15 letters relative to the baseline vs. 92.8% of those receiving combination therapy ($p = 0.001$).[51] Thus, the best treatment for myopic CNV appears to be anti-VEGF alone.

CONSENSUS GUIDELINES FOR CNV

The panel has developed a number of consensus points (Table II) and suggested treatment algorithms to guide practice patterns among medical retina experts in Singapore.

Non-AMD CNV

For extrafoveal myopic CNV, experts has agreed that laser photocoagulation is the first-line treatment (Fig. 1). The panel discussed how the presence of Foster-Fuch's spot and lacquer crack haemorrhage influence management approaches in high myopes. The presence of Foster-Fuch's spot and lacquer crack may suggest quiescent CNV, which usually does not require treatment. Fundus fluorescein angiography (FFA) may be used to distinguish between lacquer crack bleed and CNV. Increasing haemorrhage may be an indirect marker of CNV where intervention is needed. An increase in retinal thickness in OCT is also suggestive of CNV.

For juxtafoveal myopic CNV, the current literature suggests that PDT should be used as a first-line treatment.[52] Although the evidence to date has been based on case reports, there is a strong rationale for using anti-VEGFs. For subfoveal myopic CNV, PDT remains the preferred treatment modality. However, lesion size may influence treatment choice. For small lesions in early myopic CNV, both PDT and anti-VEGF work well. Lesions with a large haemorrhage or coexisting cataracts often show a suboptimal response to PDT. In these cases, first-line anti-VEGF treatment may be preferred, as there is concern regarding the long-term deleterious effects of PDT on a less healthy RPE in pathological myopia. The panel discussed the evidence supporting reduced fluence PDT and agreed that 'one fluence does not fit all'. It also agreed that patient age is an important factor for determining the urgency of treatment but not for varying the treatment protocol.

Punctate inner choroidopathy

Punctate inner choroidopathy (PIC) as a cause of CNV is often under-recognised compared with myopic CNV (Fig. 1). There is ongoing debate regarding the extent of the inflammatory component contributing to the pathogenesis of CNV in PIC. Without the guidance of large, multicentre randomised controlled trials, empirical therapies include PDT with or without subtenon or intravitreal triamcinolone acetonide, anti-VEGF therapy and combination therapy of PDT with anti-VEGF therapy.

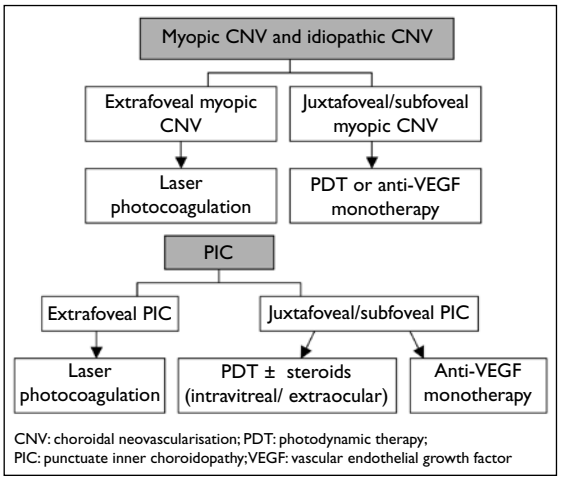

Fig. 1 Non-AMD CNV treatment algorithm.

Polypoidal choroidal vasculopathy

At present, there is a lack of strong evidence in the form of randomised clinical trials to guide our treatment of PCV. The current consensus for treatment is based on clinical experience and fairly large case series. If the polyp is distant from the fovea and the branching network is inactive, thermal laser ablation is recommended. It is likely that one can achieve quiescence for a long period of time (Fig. 2). For juxtafoveal PCV with inactive branching network, thermal laser ablation may be performed in some instances after assessing the risk of laser scar expansion and patient factors.

For subfoveal or juxtafoveal polyps with dormant, non-leaking network vessels, treatment with PDT may require an approach that is different from standard ICG-guided PDT for PCV. Although the guidelines recommend treatment to the entire network in addition to the polyps, the panel agreed that in these cases, PDT should be targeted to polyps only. Anti-VEGF is not recommended as monotherapy without PDT for such cases. For juxtafoveal and subfoveal polyps that fail to close with initial treatment, the experts suggest repeating ICG, and repeat treatment with ICG-guided PDT. In cases where the branching network is active (leaking significantly in FFA) or the polyps are near the fovea, or when the polyps are not well visualised on ICG, PDT should be administered.

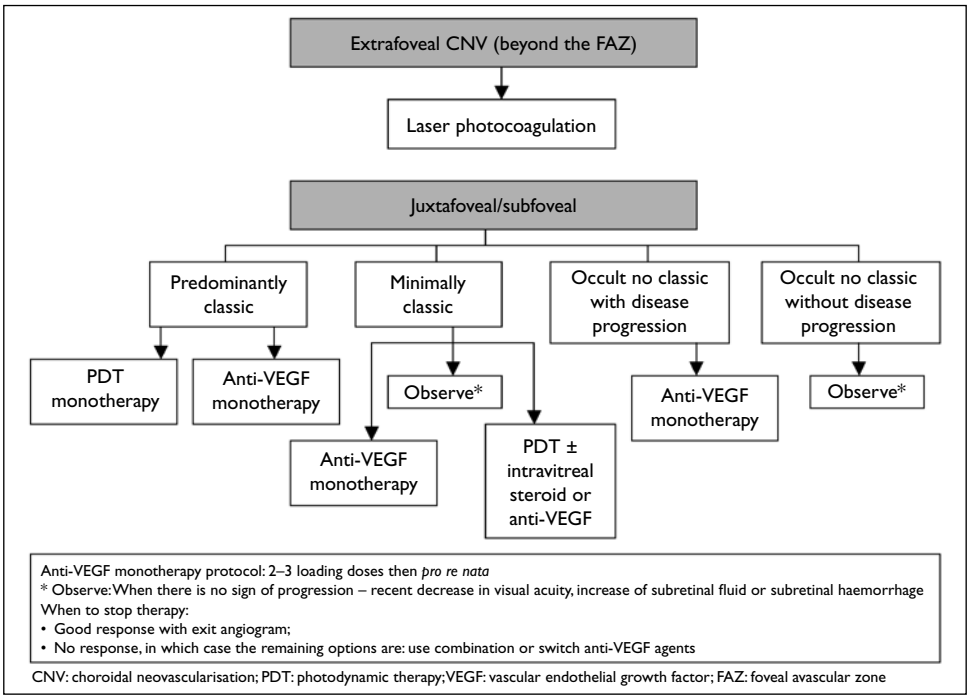

Fig. 2 CNV treatment algorithm.

In these cases, the practice is for ICG-guided PDT to include not only the polyps but also the branching vascular network.

Hence, it may be beneficial to separate the management of pure PCV (with quiescent non-leaking network vessels) from those with active, leaking branching vascular network, since the latter shares many features of CNV (polypoidal CNV, combined PCV-CNV). Confocal scanning laser ophthalmoscopy ICG is a useful imaging modality to differentiate quiescent branching vascular network from one that is active, behaving like CNV. It can be difficult to diagnose CNV associated with PCV when using flash ICG alone. For the latter, it may be advisable to treat the visible extrafoveal polyps with thermal laser in the first instance and observe the response. If repeat ICG shows successful polyp ablation but persistent macular thickening, and FFA shows continued leakage, it is reasonable to assume that leakage is emanating from a persistent branching vascular network. It may then be treated as CNV. In these cases, combination therapy (PDT plus anti-VEGF) may be beneficial for very active lesions and anti-VEGF monotherapy for less active lesions. Clinical trials would be useful to validate the management of the various subtypes of PCV.

Choroidal neovascularisation

For juxtafoveal and subfoveal CNV, the panel has reached a consensus that there is sufficient evidence to support the use of anti-VEGF therapy in all three lesion types. However, it was agreed that lesion composition (whether it is predominantly classic, minimally classic or occult with no classic) should be determined before prescribing the appropriate treatment.

For extrafoveal CNV, the panel recommends that physicians focus on the lesion perimeter based on ICG angiogram, besides FFA, as some lesions may appear subfoveal in the FFA but are actually extrafoveal on ICG angiogram. If the lesions are clearly extrafoveal on ICG angiogram, thermal laser photocoagulation may be performed (Fig. 3), and can be the definitive treatment of these cases. However, these eyes form the minority of cases.

Treatment of juxtafoveal and subfoveal classic and occult CNV with monthly intravitreal anti-VEGF injections provides the best visual outcome. However, this may not be practical or desirable in all cases due to patient preference, cost or travelling distance to and from the eye clinic. The majority of advisors follow the PrONTO protocol of three loading doses, then 'as needed' with close monitoring (approximately monthly monitoring of VA, OCT and fundus features). An angiogram is recommended after three doses for determining when to stop treatment and for monitoring of recurrences.

Combination PDT/anti-VEGF therapy has been used in an effort to reduce the number of intravitreal anti-VEGF injections in patients who may have difficulty with follow-up, or in those who reject repeated

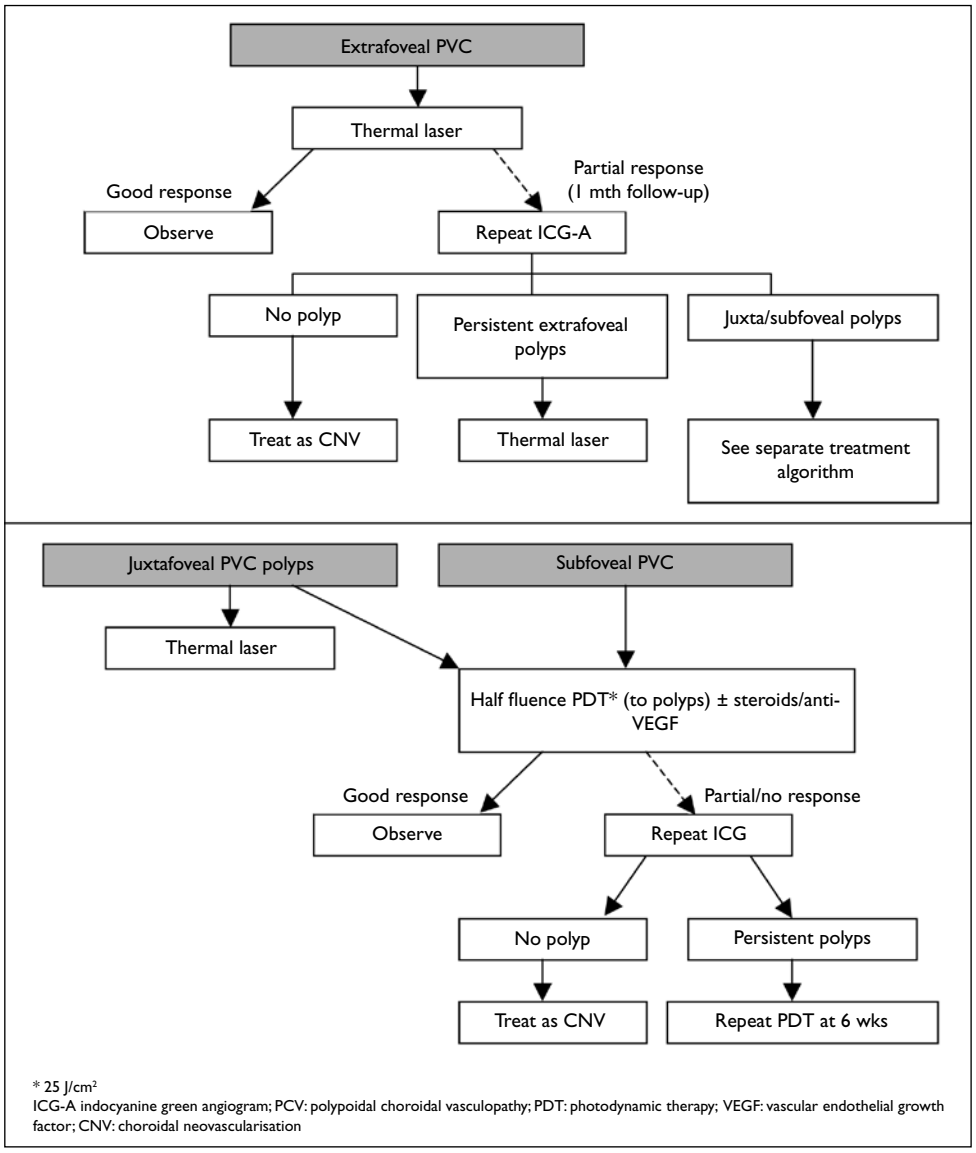

Fig. 3 PCV treatment algorithm.

intravitreal injections. It has been determined that the number of injections required was only slightly reduced and not statistically significant.[29] Nevertheless, given the practical considerations of individual patients, this treatment can be beneficial in selected cases.

CONCLUSION

Anti-VEGF therapy has greatly improved treatment outcomes in patients with CNV, and a growing body of evidence supports the role of these agents as monotherapy, with the possibility of combination therapy with PDT. The implementation of evidence-based medicine into current clinical practice is paramount to improving patient care. The treatment algorithms outlined in this review provide a structured management approach to the treatment of CNV and allied conditions such as myopic CNV and PCV, based on current evidence and clinical practice. The panel awaits the results of combination therapy trials that will provide definitive guidance on management strategies for AMD-CNV and PCV.

CONFLICTS OF INTEREST DECLARATION

Koh A, Lim TH and Au Eong KG served as advisors to Novartis. Lim TH received travel sponsorship from Novartis. Chee C received conference sponsorship from Novartis. Tan N received travel and conference sponsorship from Novartis. Wong D received travel and conference sponsorship from Novartis and Alcon, and is an advisor to Alcon. Ong SG and Yeo I declared no relevant conflicts of interest.

DISCLOSURE

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