Choroidal neovascularisation in pathological myopia: an update in management

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Choroidal neovascularisation (CNV) secondary to pathological myopia is an important cause of significant visual impairment in young and middle aged adults globally and is particularly prevalent in Asian populations. In the past few years, there have been rapid advancements in the different treatments for myopic CNV. The purpose of this perspective is to give an overview of the natural history of myopic CNV and the various treatment options including laser photocoagulation, photodynamic therapy, submacular surgery, and macular translocation surgery. Future directions in the management of myopic CNV are also discussed.

Pathological myopia is a common cause of visual impairment worldwide.1-3 High myopia is more common in Asian populations,4,5 with rates of 9-21%,6 compared with 2-4% in white people (table 1).7-9 The pathogenesis of high myopia is associated with progressive and excessive elongation of the eyeball.2,3 In highly myopic eyes, the collagen fibres are pathologically abnormal and the smaller fibres have less cross linking than those in emmetropic eyes.10-11 These factors predispose the development of various degenerative changes involving the sclera, choroid, and retina.

Vitreoretinal manifestations and lacquer cracks in high myopia

The vitreoretinal manifestations in pathological myopia are associated with varying degrees of visual loss and they include posterior staphyloma, diffuse or patchy choriotinal atrophy, retinal pigment epithelial atrophy, lacquer cracks, spontaneous subretinal haemorrhages, and macular choroidal neovascularisation (CNV).2,12-15 Lacquer cracks are formed by ruptures in Bruch’s membrane, in which small haemorrhages may develop, and predispose high myopes to rapid visual loss. Small fibrovascular tissue ingrowths may cause elevated pigmented circular lesions (Fuchs’ spots).14

Choroidal neovascularisation in pathological myopia

Incidence of myopic CNV

Macular CNV is the most vision threatening complication of myopia.15-16 It is also the most common cause of CNV in young individuals in many countries, accounting for 62% of CNV in patients aged 50 years or less in one series.7 The risk of developing myopic CNV is 5-11%.12,13 Among pre-existing myopic CNV patients, more than 30% will develop CNV in the fellow eye within 8 years.14 Clinical findings predisposing to myopic CNV include patchy chorioretinal atrophy and lacquer cracks.14

Clinical features of myopic CNV

Typically, myopic CNV is a small, flat, greyish, subretinal membrane which is less than 1 disc diameter in size14 and is located between the neurosensory retina and retinal pigment epithelium (RPE) (type 2).15 Whereas the CNV secondary to age related macular degeneration (AMD) is usually in the sub-RPE space (type 1). Most myopic CNV is subfoveal or juxtapfoveal with minimal subretinal fluid or exudate.14

Fluorescein angiographic findings of myopic CNV

Myopic CNV tends to have a classic pattern of leakage on fluorescein angiography (FA).6,14,15 With the aid of stereoscopic FA, CNV may appear as plaque-like elevation with pigmented halo and sharply defined borders. In one series, 83% (100/120 eyes) showed the classic angiographic pattern with transit phase hyperfluorescence followed by minor leakage in late phases.16

Indocyanine green angiographic findings of myopic CNV

Indocyanine green angiography (ICG-A) provides supplementary information to FA.6,14 Since myopic CNV are usually small with minimal leakage, it may be difficult for FA to distinguish CNV from mild hyperfluorescence caused by other lesions.22 ICG is minimally absorbed by RPE and blood and so allows better differentiation of CNV from other pathologies, especially if haemorrhage is present.23-25 ICG-A may also allow more precise CNV localisation and feeder vessel detection.25

Optical coherence tomographic findings of myopic CNV

Optical coherence tomography (OCT) produces high resolution cross sectional images of the retina and is useful in evaluating the morphology of various macular pathologies, including CNV.26 OCT can provide supplementary information while making treatment decisions by
Table 1: Prevalence of high myopia in different surveys and populations

<table>
<thead>
<tr>
<th>Populations</th>
<th>Surveys (year of survey)</th>
<th>Age of subjects</th>
<th>Prevalence of high myopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan Chinese</td>
<td>Nationwide survey (2000)</td>
<td>18 years</td>
<td>21.0%*</td>
</tr>
<tr>
<td>Singapore Chinese</td>
<td>Tanjong Pagar survey (1997–8)</td>
<td>49–79 years</td>
<td>9.1%†</td>
</tr>
<tr>
<td>West European</td>
<td>Rotterdam Study in the Netherlands (1990–3)</td>
<td>55 years</td>
<td>4.0%‡</td>
</tr>
<tr>
<td>Americans</td>
<td>Beaver Dam Eye Study (1988–90)</td>
<td>43–84 years</td>
<td>3.8%†</td>
</tr>
<tr>
<td>South Indian</td>
<td>Chennai Glaucoma Study (2001–3)</td>
<td>&gt;39 years</td>
<td>3.7%†</td>
</tr>
<tr>
<td>Australian</td>
<td>Blue Mountains Eye Study in Australia (1992–4)</td>
<td>49–97 years</td>
<td>1.8%†</td>
</tr>
</tbody>
</table>

*SE = −0.60 DS, †SE = +0.50 DS.

Several studies have evaluated the prognostic factors in patients with myopic CNV. In a retrospective review of 73 eyes in 63 patients with myopic CNV, patients aged more than 40 years at onset had poorer initial VA and significantly reduced VA during follow up. To determine the influence of age on the outcome, Hayashi et al demonstrated that younger patients, smaller CNV, and better initial visual acuity were more likely to have a good prognosis. Kojima et al observed that chorioretinal atrophy is the main cause of poor long term visual prognosis in myopic CNV and older age and larger CNV were factors for the atrophy.

These studies on the natural history of myopic CNV give us the clues that active interventions should be considered for patients with myopic CNV.

### Direct thermal laser photocoagulation: visual outcomes and complications

Once the only treatment, thermal laser photocoagulation is of limited benefit in myopic CNV. A study by Jalkh et al, of 19 eyes with extrafoveal CNV all had a dry atrophic photocoagulation scar a mean 29.2 months after direct thermal laser with 11% having visual improvement. In another study, laser photocoagulation resulted in complete closure of myopic CNV but VA had deteriorated in all the 16 study eyes at the final follow up. In a comparison of laser photocoagulation and natural history by Secretan et al, laser treated eyes had statistically better VA at 2 years but this difference was insignificant after 5 years. Similarly, initial beneficial effects of laser photocoagulation in juxtapfoveal myopic CNV were insignificant after 3 years in another series. Such late failure is generally due to expansion of the laser scar (atrophic creep) which is seen in 92–100% of the treated eyes. CV recurrence, which can occur in up to 72% of the treated eyes, in which 36% were subfoveal, may be due to secondary lacquer crack development.

### Photodynamic therapy with verteporfin

The selectivity and efficacy of PDT is the result of differential clearance of verteporfin in the blood and preferential binding to CNV endothelial low density lipoprotein receptors. Activation by diode laser generates reactive oxygen species which occlude abnormal CNV. Selective choriocapillary endothelial damage is the major mechanism of action of PDT. Sparing of damage to the neurosensory retina, RPE, and optic nerve makes PDT particularly useful in treating subfoveal CNV. Phase III/IV studies, as well as larger phase II/III studies, have demonstrated PDT’s ability to reduce visual loss in patients with subfoveal CNV caused by AMD and pathologic myopia.

### Subfoveal myopic CNV

The VIP study is the largest study addressing the efficacy and safety of PDT with verteporfin in treatment of subfoveal CNV caused by pathologic myopia. One hundred and twenty patients were randomised into the verteporfin treated and
placebo treated groups. At 12 months, 72% of verteporfin treated eyes compared with 44% of placebo treated eyes had a visual loss of fewer than eight letters, which was the primary outcome measure. Moreover, 14% of verteporfin treated group compared with 33% of placebo group developed moderate visual loss of 15 letters or more. The treatment benefits such as visual improvement by one line or more and better median visual acuity persisted in the second year. The primary outcome benefit, however, was not longer statistically significant by that time, which may be the result of subtle adverse effects on neurosensory retina and RPE as well as the loss of PDT efficacy (table 2).

Montero and Ruiz-Moreno also reported a series of 33 eyes with subfoveal myopic CNV treated with PDT. The mean VA improved from 0.22 at baseline to 0.26 at 12 months and those aged more than 55 had worse final vision than younger patients. Development of subretinal fibrosis after PDT correlated with the size of the CNV and refractive error. Ergun et al carried out a retrospective study on 36 eyes that had PDT for subfoveal CNV; at 2 years, 19.4% had gained three lines or more of vision, 55.6% remained stable, and 25.0% had lost three lines or more after a mean 3.2 treatments. Age and baseline VA were the only factors significantly associated with visual outcome by multivariate analysis.

In a prospective study of Asian eyes with subfoveal myopic CNV, mean best corrected VA remained at baseline levels after 24 months of follow up; 14 (63.6%) eyes had stable or improved vision while six (27.3%) eyes had gained more than one line improvement versus one line loss in controls.

Recurrent subfoveal myopic CNV after laser photocoagulation
Bandello et al retrospectively reviewed 12 eyes that underwent PDT for subfoveal recurrence after laser photocoagulation for extrafoveal myopic CNV. At 12 months, PDT treated eyes had a median two line improvement versus one line loss in controls.

Recurrent subfoveal myopic CNV after macular translocation
Macular translocation relocates the macular neurosensory retina overlying the CNV to a healthier area of RPE and choriocapillaris. Despite initial postoperative success, recurrent CNV may develop. As further focal laser photocoagulation may compromise newly translocated fovea, PDT is an option. Chan et al reported a successful single application of PDT in recurrent CNV after limited macular translocation, with complete closure, visual improvement, and no recurrence after 24 months.

**Juxtafoveal myopic CNV**
Over 75% of untreated juxtafoveal myopic CNV patients have moderate to severe visual loss within 10 years with laser photocoagulation having limited benefit because of subfoveal expansion of laser scarring. All three PDT treated juxtafoveal myopic CNV patients had visual improvement with resolution of CNV after 12–24 months. After 12 months and a mean of 2.3 PDT treatments, mean visual improvement of 1.8 lines was seen in 11 eyes with juxtafoveal myopic CNV (table 2). However, the long term safety of PDT requires confirmation since post-treatment lacquer cracks may occur predisposing to recurrent CNV and RPE atrophy with consequent adverse effects on visual outcomes.

**Extrafoveal myopic CNV**
Gelisken et al reported a series of three patients with extrafoveal myopic CNV who all had improvements in VA and complete regression of CNV after one PDT treatment and a mean follow up of 3 years.

**Submacular surgery for CNV in pathological myopia**
Submacular surgery has been evaluated for myopic CNV in several studies with differing outcomes. Most earlier studies were small case series and larger series had conflicting results. After a mean 16 months of follow up, VA improved by at least two lines in 45% and remained stable in 37% of 65 eyes with subfoveal myopic CNV in a study by Bottoni et al. Uemura et al reported 48 patients who underwent removal of subfoveal myopic CNV; VA improved in 39% and remained unchanged in 26% after a mean follow up of 24 months. However, no significant change in VA was observed in 22 patients who had removal of myopic CNV after a mean follow up of 29.3 months in Ruiz-Moreno and de la Vega’s series. Variable CNV recurrence rates of 8–57% and postoperative RPE atrophy have been reported.

**Macular translocation surgery for myopic CNV**
Machemer and Steinhorst first developed macular translocation surgery for repositioning the neurosensory retina with resolution of CNV after 12–24 months. However, no significant change in VA was observed in 22 patients who had removal of myopic CNV after a mean follow up of 29.3 months in Ruiz-Moreno and de la Vega’s series. Variable CNV recurrence rates of 8–57% and postoperative RPE atrophy have been reported.
overlying the CNV onto an area of healthier RPE and choriocapillaris. Macular translocation surgery has been performed for CNV caused by AMD as well as pathological myopia. Several surgical methods have been developed and commonly used methods are macular translocation with 360 degree retinotomy, and limited macular translocation (LMT).

**Limited macular translocation (table 3)**
LMT has the advantage of being less invasive compared with macular translocation with 360 degree retinotomy. Hamelin et al reported that patients having limited macular translocation for myopic CNV had better outcome compared with submacular surgery for CNV removal. Glacet-Bernard et al also reported the outcome of limited macular translocation for nine eyes with myopic CNV. After a mean follow up of 10 months, visual acuity improved in 67% of eyes and remained unchanged in the remaining. Ichibe et al reported the outcome of 10 patients with foveal translocation using scleral imbrication and all patients had improvement in vision after surgery. In a similar study by Fujii et al, LMT was performed in 11 eyes with myopic CNV but the results were less favourable. After a mean follow up of 9.8 months, 36% of eyes had improvement in vision, with 36% and 27% having stable or decreased vision respectively. In the series by Tano et al, 17 eyes received LMT with both scleral infolding or scleral outfording techniques. The fovea was displaced inferiorly and was completely separated spatially from the original CNV in 12 of 17 eyes (71%). Visual acuity initially improved by two lines or more in 14 eyes (82%), but the proportion dropped and only 29% could maintain the improvement of two lines or more at the final follow up. Final visual acuity was worse than best postoperative visual acuity in the majority (71%). The transient visual improvement may be jeopardised by recurrence of CNV and progressive atrophy of the retina/RPE/choroid.

**Macular translocation with 360 degree retinotomy (table 3)**
Macular translocation with 360 degree retinotomy has the advantage over LMT in allowing a greater foveal displacement. The fovea is more likely to be translocated to a healthier area with less chance of being affected in case of recurrence. The surgical steps are technically more demanding and have been described previously by Fujikado et al. Sequential or simultaneous extraocular muscle surgery are performed to counter-rotate the globe to avoid postoperative diplopia. Fujikado et al reported the results of 11 patients who underwent macular translocation with 360 degree retinotomy and simultaneous muscle surgery for myopic CNV. After a mean follow up of 6.2 months, vision improved in eight eyes with two eyes remaining unchanged and only one eye had visual loss. Seven (64%) eyes had a final visual acuity of 20/50 or better. In the extended report of 51 eyes (Ohji et al, American Academy of Ophthalmology meeting, 2004) visual improvement of three lines or more was found in 55% of eyes; stable vision and worsened vision were 25% and 20%, respectively; 47% could achieve the final vision of 20/40 or better.

One of the main disadvantages of macular translocation with 360 degree retinotomy is more extensive surgical manipulations. Complications include retinal detachment, proliferative vitreoretinopathy, postoperative diplopia, recurrent CNV, and severe hypotony. \(65\) The potential significant gain in visual acuity after surgery needs to be weighed against the manual dexterity required, complications, postoperative care, surgical costs, and facilities. Macular translocation with 360 degree retinotomy is usually considered for second eye patients with subfoveal CNV and healthy neurosensory retina.

**Other treatments for myopic CNV**
A randomised, controlled pilot study of radiotherapy over 2 years in 39 patients with subfoveal myopic CNV found a significantly smaller increase in CNV size in the treatment group and no decline in VA compared with significantly decreased vision in controls. The results, however, need to be weighed against the possible risks of malignancy and other complications after radiotherapy, particularly in younger patients. Costa et al reported using ICG mediated photothermolysis for CNV focal ingrowth sites in six patients with myopic CNV. After 48 weeks, five patients had improved and one had stable vision. No adverse events were noted. The long term efficacy of this treatment remains to be elucidated.

**PERSPECTIVES FOR THE FUTURE**
Recently, several new treatments have been proposed for CNV of AMD and many trials have been undertaken. Corticosteroids may be beneficial in patients with CNV, because of their dual anti-inflammatory and anti-angiogenic actions. The use of an intermediate acting intravitreal corticosteroid like triamcinolone acetonide in combination with PDT has been shown to be promising in treating CNV in AMD. Aneoctarve acetate is an synthetic angiotatic cortisol, but unlike triamcinolone or other corticosteroids, the glucocorticoid effect that causes cataract and elevated intraocular pressure has been removed. The drug is administered at 6 month intervals through a posterior juxtascleral route. The results were encouraging for AMD and the study demonstrated that anecortave acetate at a dose of 15 mg was safe, and statistically significant at 12 months compared with a placebo for stabilisation of vision (<3 logMAR line change), prevention of severe vision loss (decrease of ≥6 logMAR lines), and inhibition of lesion growth but was not statistically superior to the placebo for vision improvements of ≥2 logMAR lines. A pivotal trial to compare anecortave acetate and PDT with verteporfin has indicated that the two therapies were not statistically different from each other. Stabilisation of vision (<3 logMAR line change) was shown in 45% of patients with anecortave acetate, compared to 49% for PDT at 1 year follow up.

Vascular endothelial growth factor (VEGF) is responsible for ocular neovascularisation and blockade of VEGF may lead to regression of neovascularisation. Pegaptanib (Macugen) is an aptamer that is administered intravitreally every 6 weeks. It binds specifically with the VEGF\(_{165}\) isoform, and has the effects of antiangiogenesis, anti-inflammatory, and antivasular leakage. It was approved by the US Food and Drug Administration for AMD in December 2004 and it works for all types of CNV in AMD in reducing moderate and severe vision loss significantly at the 12 month follow up. Ranibizumab (rhuFab, Lucentis) is a humanised anti-VEGF antibody fragment produced by recombinant antibody production techniques. It is injected intravitreally and the
Table 3  Summary of macular translocations on the treatment of subfoveal myopic CNV

<table>
<thead>
<tr>
<th>Limited macular translocation</th>
<th>Mateo(^*) (scleral infolding)</th>
<th>Tano(^*) (both scleral infolding and outfolding)</th>
<th>Hamelin(^*) (scleral infolding)</th>
<th>Ichibe(^*) (scleral infolding)</th>
<th>Fuji(^*) (scleral infolding)</th>
<th>Ohji(^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of eyes</td>
<td>79 eyes</td>
<td>17 eyes</td>
<td>14 eyes</td>
<td>10 eyes</td>
<td>11 eyes</td>
<td>52 eyes</td>
</tr>
<tr>
<td>Mean follow up</td>
<td>24 months</td>
<td>26 months (6–18 months)</td>
<td>11 months (6–24 months)</td>
<td>15.7 months (3–28 months)</td>
<td>9.82 months (6–18 months)</td>
<td>32 months</td>
</tr>
<tr>
<td>Mean baseline VA</td>
<td>20/125</td>
<td>20/140</td>
<td>20/250</td>
<td>20/167</td>
<td>20/87</td>
<td>9.82 months</td>
</tr>
<tr>
<td>Mean final VA</td>
<td>Improved by 2.0 lines</td>
<td>Improved by 0.6 lines</td>
<td>Improved by 3.8 lines</td>
<td>Improved by 6.3 lines</td>
<td>Improved by 0.7 lines</td>
<td>Improved by 1.7</td>
</tr>
<tr>
<td>Change in VA</td>
<td>56%</td>
<td>29%</td>
<td>50%</td>
<td>100%</td>
<td>100%</td>
<td>56%</td>
</tr>
<tr>
<td>Improvement by 2 lines of more</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final VA of 20/40 or better</td>
<td>24%</td>
<td>21%</td>
<td>60%</td>
<td>9%</td>
<td>9%</td>
<td>39%</td>
</tr>
<tr>
<td>Mean foveal displacement</td>
<td>942 μm</td>
<td>1245 μm</td>
<td>695 μm</td>
<td>1170 μm</td>
<td>854 μm</td>
<td>2100 μm</td>
</tr>
<tr>
<td>Complications</td>
<td>Retinal break (21.5%), choroidal haemorrhage (3.7%), insufficient foveal displacement (20%), retinal detachment (8.8%), subfoveal recurrence (28%), macular fold (2.8%) and macular hole (1.2%)</td>
<td>Recurrence of CNV (14%), retinal detachment (14%), Macular hole (7%), transient diapla (14%), transient hyphaema (7%)</td>
<td>CNV enlargement (53%), atrophy of retina/RPE/choroid (18%)</td>
<td>CNV enlargement (53%), atrophy of retina/RPE/choroid (18%)</td>
<td>CNV enlargement (53%), atrophy of retina/RPE/choroid (18%)</td>
<td>CNV enlargement (53%), atrophy of retina/RPE/choroid (18%)</td>
</tr>
</tbody>
</table>

smaller fragment can penetrate through all layers of the retina. Ranibizumab, alone or in combination, has been demonstrated to be safe, well tolerated, and effective in reducing vascular leakage in preclinical studies.\(^9\)\(^ 9\) All potential treatments for CNV in AMD might provide strategic hopes in also treating the CNV of pathological myopia. Nevertheless, CNV with various aetiology might behave differently and might have diverse treatment complications. Further clinical trials on myopic CNV are warranted to clarify these issues.

**CONCLUSION**

Long term visual prognoses in patients with myopic CNV are relatively poor, with almost 90% having vision of 20/200 or less after 5–10 years. PDT and macular translocation surgery are effective treatments for myopic CNV, although confirmation of long term efficacy and safety await further assessment. Treatment with 360 degree macular translocation with 360 degree after treatment. Macular translocation with 360 degree translocation of long term efficacy and safety await further assessment. Are effective treatments for myopic CNV, although confirmation of long term efficacy and safety await further assessment.

**REFERENCES**


