

## PERSPECTIVE

## Alternative therapies in exudative age related macular degeneration

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Age related macular degeneration (AMD) is the leading cause of blindness in the developed world.<sup>1</sup> Vision may be lost as a consequence of choroidal neovascularisation (CNV), detachment of the retinal pigment epithelium (RPE), or geographic atrophy. Therapeutic efforts have been directed towards influencing the neovascular process, which is acknowledged to be the most common cause of visual loss.

The beneficial effect of laser photocoagulation in well defined "classic" juxtafoveal and perifoveal CNV is well established and widely accepted.<sup>2,3</sup> However, they comprise a small proportion of those with visual loss in clinical practice (<10%),<sup>4</sup> and recurrence rates of up to 59% after treatment have been reported.<sup>5</sup> At best, photocoagulation delays severe visual loss rather than representing a permanent cure in the majority of cases.

The treatment of subfoveal CNV with laser is more controversial.<sup>6-8</sup> Despite immediate loss of acuity, long term follow up of more than 2 years has shown benefit in patients with small new vessel complexes and poor visual acuity.<sup>9</sup> Nevertheless, the sudden acquisition of a dense central scotoma allows little time for the treated patients to adapt to the visual changes, and this treatment has yet to become widely practised.

There is clearly a need for new forms of treatment for subfoveal CNV in AMD, and many alternative approaches have been considered. This review outlines the current status of these alternative therapies.

### Radiation therapy

The rationale of radiation therapy is based on the observation that growing blood vessels are more sensitive to damage by ionising radiation than mature vessels,<sup>10</sup> so that new vessels may become non-perfused without damage to surrounding tissue. This can be achieved by either an external beam (teletherapy) or an episcleral plaque (brachytherapy).

In 1993, Chakravarthy and colleagues first reported a study of external beam radiation therapy in 19 AMD patients with subfoveal CNV and visual acuity no better than 6/24.<sup>11</sup> This was a non-randomised clinical trial, but seven patients who declined treatment were used for comparison. The patients received either 10 or 15 Gy in five equal fractions. Visual acuity was maintained or improved in 15 of the 19 treated patients (78%) at 6 months and 12 of the 19 (63%) 1 year following therapy, whereas only one of the seven untreated controls (14%) maintained this level of visual acuity at 1 year. No radiation induced retinopathy or optic neuropathy was reported. There was no statistically significant difference between the groups receiving either 10 or 15 Gy. Since then, a number of non-randomised clinical trials have been reported using either external beam radiation, proton beam radiation, or episcleral plaques delivering between 5 Gy to 24 Gy in

either a single fraction or up to eight fractions. The proportion whose visual acuity was maintained or improved ranged from 40% to 80% with mean follow up more than 6 months.<sup>12-14</sup>

A number of randomised prospective studies are in progress to prove the efficacy and safety of this treatment, and elective use of radiation must await the results of these trials.

### Photodynamic therapy (PDT)

Photosensitised target tissue is selectively destroyed by light at a wavelength corresponding to an absorption peak of the photosensitising agent. Photoexcitation of the photosensitiser causes conversion of the singlet ground state to the excited triplet state. Release of free radical intermediates from the triplet state causes structural and functional damage to cell membranes and other structures leading to cell death. Alternatively, the energy transfers to molecular oxygen forming singlet oxygen that reacts with proteins, lipids, and nucleic acids of the cell leading to cell death.<sup>15</sup>

Benzoporphyrin derivative monoacid (BPD) had been shown to be safe for human use in clinical trials for malignant skin tumours.<sup>16</sup> A liposomal preparation of BPD was adopted for ophthalmic work, since it was hoped that the dye would be preferentially taken up by the growing new vessels.<sup>17</sup> This photosensitiser has a long absorption wavelength at 692 nm<sup>18</sup> allowing deeper tissue penetration through blood, fluid, and fibrous tissue. In non-human primates, closure of CNV was seen in eyes 4 weeks after PDT. In eyes without CNV, the choriocapillaris was typically occluded at 24 hours after PDT with damage to the RPE in all cases. The photoreceptors showed mild pyknosis and the outer segments showed disarray and vacuolation. The medium and larger choroidal vessels and inner retina appeared normal. After 4 weeks, the choriocapillaris was reperfused; there was some functional recovery of the RPE and the photoreceptors remained mildly disorganised.<sup>15</sup>

In a phase I/II clinical trial 107 patients with CNV were treated with PDT using liposomal BPD (6 or 12 mg/m<sup>2</sup>) for subfoveal CNV. Irradiation was given 10-30 minutes after the start of the dye infusion using a diode laser (689 nm) with light doses of 600 mW/cm<sup>2</sup> and 25-150 J/cm<sup>2</sup>. At 1 week, the choriocapillaris and CNV were non-perfused. At 4 and 12 weeks, angiographic leakage reappeared in most cases with all regimens.<sup>19</sup> The same group of investigators then carried out multiple treatment in 48 patients with light doses of 100 J/cm<sup>2</sup> after the administration of 6 mg/m<sup>2</sup> of liposomal BPD at 2, 4, or 8 week intervals. Partial recurrence was still common at 12 weeks after the last treatment but the area of leakage from recurrence was reduced with retreatment and the patients maintained surprisingly good vision.<sup>20</sup> Multiple treatments using higher

dosage (12 or 18 mg/m<sup>2</sup>) of liposomal BPD in normal primates have shown significant damage to the normal retina, choroid, and optic nerve.<sup>21</sup>

It appears that PDT causes occlusion of CNV for at least a short time, and retreatment up to three times reduces area of leakage. Current randomised controlled trials will show the potential influence on visual prognosis.

### Submacular surgery with or without RPE transplantation

Advances in vitreoretinal techniques have allowed the removal of submacular CNV. In 1992, Lambert and colleagues first reported 10 cases of surgical removal of subfoveal CNV.<sup>22</sup> The postoperative visual results at 6 months ranged from 6/30 to counting fingers, with the majority having 6/60 or worse. Thomas and colleagues reported the largest series to date of 41 cases in 1994.<sup>23</sup> Only two eyes regained a visual acuity of 6/12 or better, and only 12% had an improvement of visual acuity. The final visual acuity was 6/60 or worse in 88% of the patients. These results were not obviously better than those expected from the natural history of the disease, and were disappointing when compared with results of surgery in cases with presumed ocular histoplasmosis (POHS).<sup>23</sup> Gass provided a potential explanation for this when he described two growth patterns of CNV.<sup>24</sup> In type 1 CNV the new vessels are external to the RPE, and typically occur in eyes with AMD. Type 2 CNV grows in the subretinal space, thus leaving native RPE in direct contact with Bruch's membrane. Young patients are more likely to have type 2 CNV. In the first case removal of the RPE would occur at surgery, whereas on the second the RPE would be left in situ. Furthermore, AMD is often associated with RPE dysfunction and diffuse Bruch's membrane disease when compared with focal disease in POHS. It is possible that healthy and younger RPE might recover from the surgically induced defect more readily.

Using current techniques, submacular surgery appears not to be an effective option in subfoveal CNV in AMD. RPE cell transplantation might be used to cover the defect, and has been attempted in five patients with subfoveal CNV in AMD.<sup>25</sup> All five were shown to fixate over the RPE graft immediately after surgery using scanning laser ophthalmoscope microperimetric technique. However, an absolute scotoma developed over the transplant several months postoperatively, and there was chronic oedema of the overlying retina. The RPE graft might have been rejected and destroyed, or the transplantation may not have survived on the abnormal Bruch's membrane. However, the presence of persistent oedema implies that the RPE survived since, in its absence, retinal atrophy would have been expected.<sup>26</sup> It seems most likely that the RPE survived but functioned abnormally. The key to success would be long term survival of the transplanted RPE that had normal function, which might require a healthy Bruch's membrane or an appropriate substrate. There are still a large number of hurdles to be overcome before clinical trial is appropriate.

### Drug therapy

Increasing knowledge of the properties of new vessels and their requirements for growth has given hope of alternative forms of therapy. Several approaches are available by which the behaviour of CNV might be modified by drug therapy.

#### INTERFERON

Interferon inhibits the migration and proliferation of vascular endothelial cells, which are important for angiogenesis. When administered to non-human primates with experimentally induced retinal hypoxia, interferon

caused regression of iris neovascularisation.<sup>27</sup> Based on these observations, a number of non-randomised trials showed promise. However, a prospective randomised placebo controlled trial involving 481 patients failed to demonstrate significant benefit.<sup>28</sup>

#### VASCULAR ENDOTHELIAL GROWTH FACTOR

Vascular endothelial growth factor (VEGF) has been shown to play an important role in retinal and iris neovascularisation caused by retinal ischaemia.<sup>29</sup> It is expressed in response to retinal cell hypoxia, and behaves as an endothelial specific mitogen *in vivo*.<sup>30</sup> The inhibition of VEGF by antisense prevents experimental iris and retinal neovascularisation,<sup>31,32</sup> and injection of VEGF into normal non-human primate eyes produces iris neovascularisation, neovascular glaucoma, and the proliferation of retinal blood vessels.<sup>33</sup> Anti-VEGF might play a significant role in the future management of proliferative disease as part of diabetic retinopathy, and as a result of retinal ischaemia from other causes. Its potential role in CNV in the context of AMD is less clear. Intravitreal levels of VEGF are elevated in patients with CNV,<sup>34</sup> and VEGF is present in surgically removed CNV.<sup>35</sup> RPE expression of VEGF is also increased in AMD.<sup>36</sup> Orally administered protein kinase C  $\beta$  selective inhibitor blocks VEGF induced retinal permeability.<sup>37</sup> Its use in suppressing VEGF induced angiogenesis merits further investigation.

#### INTEGRINS

There is evidence that more than one cytokine dependent pathway of angiogenesis exists, and each can be defined by its dependency on distinct vascular cell integrins. *In vivo* angiogenesis induced by basic fibroblast growth factor (bFGF) or by tumour necrosis factor alpha (TNF- $\alpha$ ) depend upon  $\alpha_v\beta_3$ , whereas angiogenesis initiated by VEGF or by transforming growth factor alpha (TGF- $\alpha$ ) are associated with expression of  $\alpha_5\beta_1$ .<sup>38</sup> Interestingly,  $\alpha_v\beta_3$  was observed on CNV from patients with AMD,<sup>39</sup> but both integrins  $\alpha_v\beta_3$  and  $\alpha_v\beta_5$  were present in retinal neovascularisation in proliferative diabetic retinopathy. Systemically administered cyclic peptide antagonist of integrins  $\alpha_v\beta_3$  and  $\alpha_v\beta_5$  not only stops vessel growth, but induces endothelial cell death in new blood vessels, and yet there is no influence on mature blood vessels.<sup>39</sup> The role of these agents in the future management of CNV is uncertain, but they hold promise.

#### THALIDOMIDE

Thalidomide is a potent teratogen causing limb defects. These effects may be consequent upon suppression of blood vessel growth in the developing fetal limb bud. It decreases the expression of integrin  $\beta$  subunits, most notably  $\beta_3$  and  $\beta_2$ .<sup>40</sup> Orally administered thalidomide inhibits corneal neovascularisation in rabbit.<sup>41</sup> However, thalidomide has to be given intraperitoneally to inhibit VEGF induced corneal neovascularisation in rodents.<sup>42</sup> Its role in treating or prevention of CNV has yet to be tested.

### Prophylactic treatment

AMD is difficult to treat once CNV is established. In future, prevention of visual loss might be achieved by prophylaxis to prevent the formation of CNV. This could be directed to those with age changes at the level of Bruch's membrane known to imply high risk of visual loss. Many clinicians have observed that drusen disappear after focal laser therapy to the posterior pole.<sup>43</sup> As CNV is believed to occur in response to age change in Bruch's membrane, resolution of these changes might intuitively be expected to lower the incidence of CNV. The idea of using a small number of threshold laser spots to cause resolution of

drusen, and as a prophylactic therapy for AMD, has attracted considerable interest. In one study such patients were treated with 12 argon laser lesions in the posterior pole, with review for 12–24 months.<sup>44</sup> CNV developed in one patient 8 months after treatment, with consequent loss of central vision. One patient lost three lines of vision due to geographic atrophy after 12 months. In nine of the remaining 10 patients, high risk characteristics of drusen were reduced, and maintained 6/12 visual acuity at 12 months.

The CNV prevention trial is a multicentre randomised prospective trial using up to 40 laser spots for treating high risk eyes in AMD patients.<sup>45</sup> In the initial report of 276 patients, age changes, such as drusen, were modified by the therapy, but there was an increase rate of CNV formation with no benefit to visual acuity at 12 months. By contrast, a controlled study undertaken in Sweden appeared to show benefit, although the control group had a surprising high incidence of visual loss.<sup>46</sup>

### Conclusion

Many forms of treatment have been devised with the objective of destroying or suppressing subretinal new vessel growth. None of these is likely to have a significant impact on blindness due to AMD. There is urgency to identify the new therapeutic avenues. It appears likely that good vision will depend upon survival of the RPE/photoreceptor complex. Any therapeutic agent or manoeuvre directed against new blood vessels must not interfere with the limited potential for RPE repair. Thus, the success of a medical agent would depend upon its ability to suppress blood vessel growth or cause endothelial cell death without associated effect on the RPE.

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