ARTICLE

Neovascular age-related macular degeneration: present and future treatment options

MARCELA VOTRUBA, ZDENEK GREGOR

Abstract

Purpose **To review treatment strategies in neovascular age-related macular degeneration (ARMD).**

Methods **Medline and Embase search.**

Results **Age-related macular degeneration (ARMD) is the commonest cause of blindness in the developed world in individuals over 50 years of age. ARMD may lead to loss of vision by atrophy of the retinal pigment epithelium or by the development of choroidal neovascular membranes (CNVM) under the macula, which leak serous fluid and blood and ultimately cause a blinding disciform scar. Treatment options currently being investigated fall into three main approaches: elimination of the CNVM from the subfoveal area (by laser or surgery), modification of the CNVM (by laser, radiotherapy or chemotherapeutic agents) or lastly prevention of the formation of CNVM (by laser prophylaxis, diet or gene targeting). Whilst almost no therapy restores normal visual acuity, any significant visual improvement over the natural history may be regarded as beneficial.**

Conclusions **Both the current and immediate future potential therapies for choroidal neovascularisation in ARMD require considerable advances to be made before they will make any impact on blindness caused by ARMD. Of the current treatments none are curative and the treatment benefits are small. There is an urgent need for new therapies.**

M. Votruba
Z. Gregor
Moorfields Eye Hospital
London EC1V 2PD, UK

M. Votruba
Institute of Ophthalmology,
UCL
London EC1V 9EL, UK

Mr Zdenek Gregor, FRCS, FRCOphth ✉
Moorfields Eye Hospital
City Road
London EC1V 2PD, UK
Tel: +44 (0)20 7253 3411, ext 2022
Fax: +44 (0)20 7253 4696
e-mail: zdenek.gregor@moorfields.nhs.uk

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Age-related macular degeneration (ARMD) is the commonest cause of blindness in the developed world in individuals over 50 years of age.[1,2] It is estimated that 1.6% of the population in the 50- to 65-year-old age group is affected, rising to 30% in the over-75-year-old age group. In the UK there are 16 000 new cases per year. By the year 2030, 20% of the population of the USA will be over 65 years of age.[3] The impact of ARMD on individuals and on health care delivery is therefore set to increase.

The implications of untreatable ARMD in terms of morbidity, social and health care costs and personal misery are considerable. We as ophthalmologists may not always grasp the enormity of the effect of ARMD on the patient's quality of life. There is evidence of a difference in perception between ophthalmologists and patients regarding the quality of life associated with ARMD. Recently, Brown *et al*.[4] attempted to assess quality of life issues in ophthalmologists and patients with ARMD by utility analysis using the time trade-off method (trade years of remaining life in return for perfect vision) and the standard gamble method (risk of dying in return for perfect vision) for various degrees of theoretical visual loss secondary to ARMD. A utility of 1.0 is associated with perfect health and a value of 0.0 is associated with death. The ophthalmologists were significantly less willing than the patients to trade years of life for perfect vision and were less willing to take the risk of dying in return for perfect vision, suggesting a considerable degree of potential adjustment to life without central vision in certain individuals.

However, ARMD causes a substantial decrease in patient utility values and is highly dependent on the degree of visual loss in the better-seeing eye.[5] Patients with visual acuities of 20/20 to 20/50 in the better-seeing eye were willing to trade 11% of their remaining lifetime in return for perfect vision in each eye, whereas patients with visual acuity of counting fingers to light perception were willing to trade 60% of their remaining lifetime in return for perfect vision in each eye.

A change in utility value induced by an interventional treatment can be amalgamated with the duration of the treatment effect to provide a number of quality-adjusted life-years (QALYs) gained by a specific treatment (QALYs = |gain in utility value| × |duration of treatment effect|). The number of QALYs gained by a treatment can then be incorporated with medical costs, to arrive at a final figure: the cost per QALY. This parameter can be used to compare the cost-effectiveness of treatments.[6] Unfortunately, the impact of ARMD and the various treatments used on the quality of patients' lives has not been studied sufficiently.

ARMD may lead to loss of vision by atrophy or by the development of abnormal choroidal neovascular membranes (CNVM) under the

retina, which leak serous fluid and blood and ultimately cause a blinding disciform scar. Overall 10–20% of patients with ARMD exhibit the exudative form but exudative ARMD associated with choroidal neovascularisation is responsible for 90% of severe visual loss in patients with ARMD. Most therapeutic interventions currently, and in the foreseeable future, are aimed at modifying the neovascular process in order to prevent further loss of visual acuity and central vision and to preserve the ability to read.

Treatment options

The most promising modalities being investigated for the treatment of ARMD include novel laser therapies (photodynamic laser therapy, PDT), surgery (submacular and macular translocation surgery), radiation (external beam/teletherapy or episcleral plaque/brachytherapy), chemotherapeutic agents (angiogenesis inhibitors such as thalidomide, interferon, integrins and vascular endothelial growth factor inhibitors), gene therapy and transplantation of retinal pigment epithelium and photoreceptors.[7]

Present and future treatment options may be divided into three main approaches: elimination of the CNVM from the subfoveal area (by laser or surgery), modification of the CNVM (by laser, radiotherapy or chemotherapeutic agents) or lastly prevention of the formation of CNVM (by laser prophylaxis, diet or gene targeting).

Elimination of neovascularisation

Laser photocoagulation therapy of extrafoveal or juxtafoveal CNVM

The only well-studied and established treatment option currently is focal argon laser photocoagulation of the CNVM, whose beneficial effect in classical juxtafoveal and perifoveal CNVM was established by the Moorfields Macular Study Group[8] and the Macular Photocoagulation Study Group (MPS).[9–13]

However, less than 10% of patients presenting with ARMD will have CNVM of the appropriate type to be suitable for treatment under the MPS criteria. Of those who are, 50% will have subfoveal CNVM at presentation, and fall into the more controversial treatment group, requiring sight-threatening subfoveal laser photocoagulation.[11] Of those who are suitable for treatment of perifoveal or juxtafoveal CNVM the persistence or recurrence rate is disappointingly high (over 50% at 2 years).[10] Recurrent neovascular lesions tend to be subfoveal. Complications of laser include Bruch's membrane rupture, haemorrhage and retinal pigment epithelium (RPE) rips and inadvertent photocoagulation of the fovea, which can lead to unexpected visual loss.

Laser photocoagulation therapy of subfoveal CNVM

In 1991 the MPS group reported that eyes treated by focal argon photocoagulation of CNVM showed prevention of large decreases in visual acuity after 2 years follow-up.[10] The benefits of laser treatment persisted through at least 4 years of follow-up.[11] For subfoveal lesions which are small or medium in size with classic CNVM and moderate or poor initial visual acuity, focal laser offers the possibility of prevention of catastrophic visual loss associated with end-stage disciform scarring, but at the costs of immediately producing a central scotoma.[13] In spite of these conclusive data many clinicians prefer not to treat subfoveal CNVM.

The incremental cost-effectiveness of laser photocoagulation for subfoveal choroidal neovascularisation has been evaluated by Brown *et al*.[14] Surprisingly, they found that laser photocoagulation for subfoveal choroidal neovacularisation resulted in a mean gain of 0.257 QALYs per treated patient, as compared with no treatment, and the resultant $/QALY gained was $5629. This result, which takes into account patient preference-based utility data, compares quite favourably with other therapies across different medical specialties and most probably with all other modalities of therapy of subfoveal CNVM discussed below.

Extraction of CNVM, translocation surgery and RPE transplantation

The two new techniques of surgical extraction of CNVM and macular translocation surgery have shown poor visual results in pilot studies, secondary to loss of normal RPE/Bruch's membrane anatomy.

Extraction of CNVM

Small studies of the surgical removal of the neovascular net with or without transplantation of RPE or iris pigment epithelium cells are reported.[15,16] The results, however, are disappointing, with few patients experiencing improvement in visual acuity.[17,18] The concurrent removal of RPE cells in submacular surgery appears to limit the final visual outcome,[19] making this type of surgery ineffective in subfoveal CNVM in ARMD. Human fetal RPE transplantation may offer a solution, but remains problematic.[15] Humayun *et al*.[20] undertook the transplantation of fetal retinal photoreceptor suspensions into the subretinal space in 9 subjects, 1 of whom had ARMD. They could not demonstrate a definite positive effect on visual function but found good tolerance of the graft and this work is continuing. Transplantation of autologous iris pigment epithelium after removal of CNVM has also been reported in a pilot study[21] and suggests that these cells may be used as a substitute for autologous RPE cells for transplantation to the subretinal space.

The National Institutes of Health in the United States sponsored randomised Submacular Surgery Trials to evaluate the efficacy of surgical removal of CNVM, and

have reported pilot study data on ophthalmic outcomes[22] and quality of life outcomes.[23] The ophthalmic outcomes suggest that there are few treatment complications in the 70 patients enrolled. At 2 years 20 of 30 eyes (65%) in the laser arm and 14 of 28 study eyes (50%) in the surgery arm had visual acuity that was better than or no more than 1 Snellen line worse than the baseline level.

Macular translocation

Macular rotation or translocation surgery is another surgical approach being investigated.[24,25] It is a technically more difficult procedure and may fail if there is insufficient translocation, recurrence of the CNVM or the development of cystoid macular oedema. Surgery is required to correct the torsional complications and the patient may need multiple operations. Pieramici *et al.*[26] have described a limited macular translocation technique with some success and data on 102 eyes with 3 and 6 months follow-up. At 3 and 6 months 37% and 48% of the study group, respectively, experienced 2 or more Snellen lines of improvement on visual acuity testing, and by 6 months 16% experienced greater than 6 lines of visual improvement. Complications associated with limited macular translocation reported in 153 consecutive eyes of 151 patients include retinal detachment (17.4%), retinal breaks (13.4%), macular holes (7.8%), macular fold (4.6%) and intraocular haemorrhage (9.2%).[27] At least one complication occurred in 53 of 153 eyes (34.6%) and in 51 of these 53 eyes (96%) the complications occurred before 3 months of post-operative follow-up.

Modification of the neovascularisation process

Photodynamic therapy

Trials of photodynamic therapy (PDT) for CNVM in ARMD offer some hope for patients with subfoveal CNVM. PDT would appear to be a relatively selective form of treatment for choroidal neovascularisation. Unlike standard focal laser photocoagulation, PDT can close choroidal neovascularisation with minimal or no detectable damage to surrounding tissues, although it is not entirely clear, even from animal studies in monkeys, how exactly it works.[28] Several dyes are under investigation. Most data are now available with Visudyne and there is now mounting evidence that PDT can reduce the risk of visual loss in eyes with subfoveal CNVM from ARMD.

Results of the 2 year follow-up of PDT with verteporfin for subfoveal choroidal neovascularisation in ARMD have been reported recently.[29] The authors conclude that the beneficial outcomes with respect to visual acuity and contrast sensitivity at the 12 month examination in verteporfin-treated patients were sustained through the 24 month examination.[30] At 12 months participants had received an average of 3.4 treatments. Overall, for all patients, 61.2% of eyes treated with verteporfin and 46.4% of eyes treated with placebo lost fewer than 15 letters of vision ($p < 0.001$). Of patients with predominantly classic CNVM (area of CNVM at least 50% of the area of whole lesion), 33% of the eyes given verteporfin and 61% of the placebo-treated eyes lost 15 or more letters (or 3 Snellen lines) of vision. At 24 months, 53% of verteporfin-treated patients compared with 38% of placebo-treated patients lost fewer than 15 letters ($p < 0.001$). Subgroup analysis for patients with predominantly classic CNVM showed 59% of verteporfin-trated patients compared with 31% of placebo-treated patients lost fewer than 15 letters ($p < 0.001$). Patients with minimally classic lesions (area of classic CNVM less than 50% but more than 0% of the lesion) showed no statistically significant difference in visual acuity.

Although these results are encouraging, there are still many unanswered questions regarding PDT in practice, such as the frequency of retreatment required, standardisation of the interpretation of fluorescein angiograms of classic and occult components of CNVM, long-term results and quality of life issues. Further multicentre randomised controlled trials are likely to be helpful.

Photochemical and thermal methods

Transpupillary thermotherapy (TTT) for ARMD has yet to be subjected to a randomised controlled trial and the optimal treatment parameters have not been established.[31] Nevertheless, a recent retrospective, case-selected, open-label trial of 44 eyes of 42 patients with CNVM secondary to ARMD treated by diode laser (810 nm) TTT has shown encouraging results.[32] Predominantly classic membranes were closed in 75% of eyes and remained persistent in 25%, with no recurrences over a mean follow-up of 6.1 months. Predominantly occult membranes were closed in 78% of eyes, remained persistent in 13% and were recurrent in 5%.

Radiotherapy

External beam (teletherapy) and episcleral plaque (brachytherapy) therapy are still being investigated as modalities for the treatment of neovascularisation in ARMD. The rationale for the use of ionising radiation is based on the observation that radiotherapy inhibits vascular endothelial cell proliferation *in vitro* and prevents angiogenesis *in vivo*,[33,34] hence growing blood vessels may become non-perfused whilst mature vessels remain unaffected.[35] Radiotherapy also reduces inflammation and scarring.[36,37]

A pilot study by Chakravarthy *et al.*[38] showed a beneficial effect of radiotherapy. Since then other studies have been performed, with conflicting results. Since phase 1 trials have given an indication that radiotherapy may have a role, large-scale, multicentre, randomised controlled clinical trials have been undertaken. To date there is no compelling evidence that radiotherapy preserves vision in ARMD,[39] although one trial shows a favourable outcome at 2 years for small CNVM and in patients with better visual acuity at the outset.[40] A number of other randomised controlled trials have found

no evidence of an effect of external beam radiation on the risk of moderate visual loss in exudative ARMD within 1 year.[41–44] The results of 2 year follow-up trials are awaited. Further evaluation of the treatment effects of higher doses of radiotherapy is under way at the National Eye Institute, Bethesda, MD.

Chemotherapeutic agents

Angiogenesis inhibitors such as interferon, thalidomide, integrins and vascular endothelial growth factor (VEGF) inhibitors are arousing considerable scientific interest for their potential in the treatment of neovascular ARMD. Potentially, they could be administered systemically or locally, into the vitreous or under the retina.

Interferon has an inhibitory effect on the migration and proliferation of vascular endothelial tissue but interferon alpha-2a given subcutaneously has failed to show any therapeutic effect.[45,46] Indeed, in the only large multicentre, double-masked randomised controlled trial reported, patients treated with three injections per week for 52 weeks were more likely to have lost at least 3 Snellen lines of vision than those treated with placebo (absolute risk 50% vs 38%).[45] There appears to be significant toxicity, including fatigue, influenza-like symptoms, gastrointestinal symptoms and central nervous system symptoms.

Thalidomide, which is a powerful teratogen, is anti-angiogenic.[47] The effect of thalidomide, administered systemically, is being investigated in CNVM in a randomised controlled trial, in combination with laser photocoagulation.

Intravitreal triamcinolone may provide short-term improvement of vision but these results are preliminary and based on a single injection in 27 patients followed up for 6 months;[48] a randomised controlled trial is under way. Penfold *et al.*[49] and Challa *et al.*[50] reported small uncontrolled trials of triamcinolone with some favourable effects on vision up to 18 months of follow-up.

Prevention of the neovascular response

Prophylactic laser to drusen

It is estimated that 12.4% of patients in the USA with bilateral soft drusen develop unilateral or bilateral CNVM within 10 years.[51] Laser treatment in subjects with high-risk clinical features of ARMD has been shown to lead to the resolution of drusen.[52] The Choroidal Neovascular Prevention Trial Research Group, a multicentre, randomised clinical trial of laser versus observation, has addressed the question of short-term effects[53] and improvements in visual function at year 1[54] and 2 years.[55] Laser-induced drusen reduction in eyes with non-exudative ARMD is associated with improved visual acuity ($p < 0.001$) and contrast sensitivity in eyes at 1 year. CNVM formation was, however, similar in treated and untreated eyes through 24 months of follow-up.

Diet and other risk factors

It has been proposed that antioxidants may prevent cellular damage in the retina by reacting with free radicals produced in the process of light absorption. There is some evidence that low levels of lutein and zeaxanthin may be associated with an increased risk of ARMD.[56] Despite a number of trials in this area there is no conclusive evidence that dietary supplementation with vitamins, minerals or trace elements leads to a decrease in visual loss secondary to ARMD.[57] Future therapies may involve the manipulation of these substances.

Future treatments

Much of our hope for successful future treatments of CNVM in ARMD lies in the areas of suppression or modification of the neovascular response with novel anti-antiogenic factors and gene therapy. Pilot studies and trials of anti-VEGF are under way. Restoration of the normal anatomical relationships between photoreceptor, Bruch's membrane and RPE is the goal.

Gene therapy, in which a functioning gene is inserted into human cells to correct a genetic error or to introduce new function for therapy, may offer another avenue for future therapy.[58] Recently, human RPE cells transduced with retroviral beta-galactosidase (as a marker) and bovine choroidal endothelial cells transduced with retroviral tissue inhibitor of metalloproteinase-2 (TIMP-2) were transplanted by subretinal injection into monkey retina which had CNV lesions induced by laser. The cells survived for at least 14 days in the subretinal space and continued to express TIMP-2. The endothelial cells showed a decreased angiogenic response to vascular endothelial growth factor (VEGF), namely decreased migration and tube formation in the induced CNV lesions. The authors believe that this pilot is encouraging for the possibility of gene therapy for the treatment of choroidal neovascularisation.[59]

Conclusion

Both the current and immediate future potential therapies for choroidal neovascularisation in ARMD require considerable advances to be made before they will make any impact on blindness caused by ARMD. Of the current treatments none are curative and the treatment benefits are small. There is an urgent need for new therapies.

It has been tempting to try any new class of drug or therapy, conventional or alternative. Sadly this serendipitous approach is unlikely to succeed. A more rational approach may be to further our understanding of the underlying pathophysiology of this condition and, from this, design a logical research and treatment strategy. Patients and clinicians may have to be patient.

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