Clinical review

Extracts from "Clinical Evidence"

Age related macular degeneration

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Interventions

Beneficial:

Thermal laser photocoagulation

Photodynamic treatment with verteporfin

Unknown effectiveness:

Proton beam and scleral plaque radiotherapy

Submacular surgery

Unlikely to be beneficial:

External beam radiation

Ineffective or harmful

Subcutaneous interferon alfa-2a

Background

Definition Age related macular degeneration is the late stage of age related maculopathy. It has two forms: atrophic (or dry), characterised by geographic atrophy, and exudative (or wet), characterised by choroidal neovascularisation, which eventually causes a disciform scar.[1 2]

Incidence/prevalence Age related macular degeneration is the commonest cause of blind registration in industrialised countries. The atrophic form is more common than the more sight threatening exudative form, affecting about 85% of people with age related macular degeneration.[3] End stage (blinding) age related macular degeneration is found in about 1.7% of all people aged over 50, and incidence rises with age (0.7-1.4% in people aged 65-75, 11.0-18.5% in people aged over 85).[4–6]

Aetiology/risk factors The aetiology is multifactorial. Age is the strongest risk factor. Ocular risk factors for the development of exudative age related macular degeneration include the presence of soft drusen, macular pigmentary change, and choroidal neovascularisation in the other eye. Systemic risk factors are hypertension, smoking, and positive family history.[7 8] A role for diet and exposure to ultraviolet light is suspected but unproved.

Prognosis Age related macular degeneration impairs central vision, which is required for reading, driving, face recognition, and all fine visual tasks. Atrophic age related macular degeneration progresses slowly over many years, and time to legal blindness (visual acuity $<20/200$) is highly variable (usually about 5-10 years).[9 10] Exudative age related macular degeneration is more threatening to vision and is responsible for 90% of severe visual loss in people with age related macular degeneration. It usually manifests with a sudden worsening and distortion of central vision. It progresses rapidly (typically over weeks or months) until scarring is complete and no further vision is lost, at which point legal blindness has usually been reached. Most people (estimates vary from 60% to 90%) with exudative age related macular degeneration progress to legal blindness and develop a central defect (scotoma) in the visual field.[11–14] Peripheral vision is preserved, allowing the person to be mobile and independent. The ability to read with visual aids depends on the size and density of the central scotoma and the degree to which the person retains sensitivity to contrast. Once exudative age related macular degeneration has developed in one eye, the other eye is at high risk (cumulative estimated incidence 10% at one year, 28% at three years, and 42% at five years).[7]

Aims To minimise loss of visual acuity and central vision; to preserve the ability to read with or without visual aids; to optimise quality of life; to minimise adverse effects of treatment.

Outcomes Visual acuity, rates of legal blindness, contrast sensitivity, quality of life, appearance of retina on fluorescein angiography, rate of adverse effects of treatment. Visual acuity is measured using special eye charts, usually the early treatment of diabetic retinopathy study (ETDRS) chart, although many studies do not specify which chart was used. Stable vision is usually defined as loss of two lines or less on the ETDRS chart. Moderate and severe visual loss are defined as a loss of more than three and six lines respectively, corresponding to a doubling and quadrupling of the vision angle. Loss of vision to legal blindness ($<20/200$) is also used as an outcome. A reading of 20/200 (or 6/60 in metric) on the Snellen chart means that a person can see at 20 yards (or 6 metres) what a normally sighted person can see at 200 yards (or 60 metres).

Methods *Clinical Evidence* search and appraisal December 1999. All randomised controlled trials (RCTs) were included, but small early RCTs were

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excluded when larger, more recent trials were available.

Question: What are the effects of treatments for exudative age related macular degeneration?

Option: Thermal laser photocoagulation

Summary Four large RCTs have found that laser photocoagulation decreases the rate of severe visual loss and preserves contrast sensitivity in selected people with exudative age related macular degeneration (those with well demarcated lesions). Choroidal neovascularisation recurs within two years in about half of those treated. Photocoagulation may reduce visual acuity initially.

Benefits

We found no systematic review. **Versus no treatment:** We found four large unblinded multicentre RCTs of laser photocoagulation versus no treatment in a selected population.[11–17] We also found four smaller RCTs that included a wider range of people.[18–21] All four of the large trials found that treatment conferred clinically and statistically significant benefit, in terms of reduced risk of severe visual loss (defined as loss of six or more lines on the special eye chart), which persisted beyond three years. Participants differed in terms of the position of the choroidal neovascularisation on the retina, whether far, near, or under the centre of fixation (extrafoveal,[11 13] juxtafoveal,[14 15] or subfoveal[12 16 17]). In the study of extrafoveal choroidal neovascularisation, treatment was beneficial despite the fact that 19% of eyes randomised to observation later received laser treatment.[13 11] Reanalysis of people with juxtafoveal choroidal neovascularisation found that benefit was limited to those with pure classic lesions (no occult element) on fluorescein angiography (52% of randomised eyes), who were more than twice as likely to avoid developing severe visual loss than were people receiving no treatment (odds ratio 2.2, 95% confidence interval 1.4 to 3.4 at three years). The two trials in people with subfoveal choroidal neovascularisation found benefit from treatment despite an immediate loss of vision in the treated groups (average three lines on the special eye chart).[12] At five years after treatment, rates of recurrence of choroidal neovascularisation ranged from 39% to 76%, with most occurring within two years. Of the four smaller RCTs, one found that fovea sparing laser photocoagulation preserved visual acuity compared with no treatment.[18] The other three found that scatter (non-confluent) laser was no better than no treatment in occult choroidal neovascularisation. However, the trials were too small to rule out a beneficial effect. **Different wavelengths:** We found three large multicentre RCTs that compared two wavelengths of laser (krypton red or argon green) for photocoagulation of choroidal neovascularisation in age related macular degeneration.[22 23] All found no significant difference in outcome. **Effects in people with choroidal neovascularisation identified by indocyanine green angiography:** We found no RCTs. Uncontrolled case series have reported good outcomes in selected people.

Harms

Laser destroys new vessels and surrounding retina, and the resultant scar causes a corresponding defect in the central visual field. If the laser is applied to subfoveal lesions, or if the laser burn spreads to the fovea, visual acuity will be impaired; two of the RCTs described immediate loss of visual acuity (an average loss of three lines on the special eye chart).[12 17] We found no evidence of other adverse effects.

Comment

The benefits of laser photocoagulation depend on accurate, complete treatment, requiring high quality angiography and trained, experienced practitioners.[11–17] The risk of immediate loss of visual acuity with laser photocoagulation may limit its acceptability.

Option: Radiotherapy

Summary Three RCTs found no evidence of an effect of external beam radiation on the risk of moderate visual loss in people with exudative age related macular degeneration within one year. We found insufficient evidence on long term safety, but one RCT found no evidence of an association with cataract formation at one year.

Benefits

We found no systematic review. **External beam radiation:** We found three RCTs. The first trial, a large multicentre double blind RCT, compared external beam radiation (16 Gy in 2 Gy fractions) delivered to the macula against no treatment in 205 people with new subfoveal choroidal neovascularisation.[24] The control group received "sham" radiation treatment (eight fractions of 0 Gy). At 12 months, 51.1% of treated people and 52.6% of controls had moderate visual loss, defined as loss of three or more lines on a special eye chart ($P = 0.88$). No treatment benefit was detected for subgroups of patients classified on the basis of fluorescein angiographic appearance into classic and occult lesions. The second trial, a small, single blind RCT, compared external beam radiation (24 Gy in 6 Gy fractions) delivered to the macula against no treatment in 74 people with new subfoveal choroidal neovascularisation.[25] At 12 months, there was no significant difference between treated and untreated people in terms of their risk of moderate or severe visual loss (defined as losses of three or six lines on the special eye chart): the absolute risk of moderate visual loss was reduced by 20% with treatment, but the confidence interval spanned zero (absolute risk −20%, −44% to 4%). The third RCT was a small single blind randomised pilot study comparing single fraction external beam radiation of 7.5 Gy against no treatment in 27 people.[26] No treatment benefit was detected over a mean follow up of 17 months (range 7-32 months). **Other techniques:** We found conflicting and inconclusive evidence from non-randomised pilot studies using proton beam and scleral plaque (local) radiotherapy in a variety of dosing and timing schedules.

Harms

All RCTs reported no adverse effects after 12 months. Uncontrolled pilot studies suggest that the main risks using current dosing and delivery techniques are cataract (2 of 41 people in one series[27]) and transient keratoconjunctivitis with epiphora (10 of 75 in one series[28]). However, the large multicentre RCT found no significant difference in cataract formation between treated and untreated people at 12 months (10% treated *v* 16% control) or dry eye symptoms (40% treated *v* 45% control).[24] Doses of up to 25 Gy delivered in daily fractions of 2 Gy or less are generally claimed not to cause damage to the retina or optic nerve. However, radiotherapy is potentially toxic to the retina, optic nerve, lens, and lachrymal system, with toxic effects sometimes manifesting two years after treatment.[29] A two centre case series of people treated with external beam radiation reported an abnormal choroidal vascular growth pattern associated with macular bleeding and exudation and marked loss of visual acuity.[30] This change was detected in 12.6% of 95 people and 7.1% of 98 people 3-12 months after radiotherapy and may explain the lack of treatment benefit.

Comment

One multicentre RCT of radiation for age related macular degeneration is under way (U Chakravarthy, personal communication, 1999). Trials with less than two years' follow up may miss important adverse effects.

Option: Submacular surgery

Summary We found insufficient evidence on the effects of submacular surgery. Rates of recurrent choroidal neovascularisation are high, and there is a clinically significant risk of ocular complications resulting in visual loss and further surgical intervention.

Benefits

We found no systematic review. **Versus no treatment:** We found no RCTs. **Versus laser photocoagulation:** We found one pilot RCT (n=70) comparing submacular surgery against laser photocoagulation for recurrent subfoveal choroidal neovascularisation (S Bressler, Macular Society Meeting, San Francisco, 1999). It found no significant difference between the two treatment groups. **Versus alternative surgical techniques:** We found one RCT in 80 eyes with exudative age related macular degeneration comparing surgery plus subretinal injection of tissue plasminogen activator against surgery plus subretinal injection of a control solution.[31] The trial found no significant difference in visual or anatomic outcome.

Harms

Submacular surgery can have effects that threaten vision or require further surgical intervention. However, we found no good data on the frequency of adverse events. The largest case series of people with age related macular degeneration and non-age related macular degeneration reported cataract formation (in up to 40%), retinal detachment (5-8%), recurrent new vessel formation (18-35% within 12 months), and macular complications (haemorrhage and pucker; no rates given).[32]

Comment

Most evidence for submacular surgery currently comes from small uncontrolled case series (<50 people with age related macular degeneration) with short follow up, often including people with other types of macular degeneration. These found that few people with age related macular degeneration experienced improved vision with surgery.[29 32] Comparing results is difficult because of evolving surgical techniques, changes in outcome measures, and variations in follow up. A large non-blinded RCT is currently recruiting and will compare standardised surgical technique against no treatment in new and haemorrhagic choroidal neovascularisation in people with age related macular degeneration (S Bressler, personal communication, 1999). Other surgical techniques are being developed in volunteers, including macular translocation and retinal pigment epithelial transplantation, but these have yet to be formally evaluated.

Option: Subcutaneous interferon alfa-2a

Summary One large RCT found no evidence of benefit from subcutaneous interferon alfa-2a (an antiangiogenesis drug) and found evidence of serious ocular and systemic adverse effects.

Benefits

We found no systematic review. We found one multicentre, double blind RCT in 481 people with subfoveal choroidal neovascularisation due to age related macular degeneration.[32] This compared three doses of subcutaneous interferon alfa-2a (1.5, 3, and 6 mIU given three times a week for one year) against placebo. At 52 weeks, treatment at all doses was associated with a higher risk of losing at least three lines of vision on the Snellen chart compared with placebo (absolute risk 50% *v* 38%, increase 12%, 0% to 23%). No benefit was found for secondary end points or in subgroups of patients.

Harms

Adverse effects of interferon alfa-2a were common and potentially severe in this and other poorer quality RCTs. These included fatigue and influenza-like symptoms as well as gastrointestinal symptoms and effects on the central and peripheral nervous system. Although at least one adverse event was reported in 86% of people taking placebo, the proportion of people on active treatment who suffered adverse effects increased with dose, as did the severity of adverse effects. Up to 5% of treated people experienced retinopathy induced by interferon alfa-2a,[33] perhaps accounting for worse visual outcome in treated people.

Comment

There is widespread interest in safe, effective antiangiogenesis drugs as prophylaxis for exudative age related macular degeneration. Several drugs are currently under preclinical and early phase clinical study. RCTs are currently investigating thalidomide with and without concurrent laser photocoagulation, and intravitreal triamcinolone.

Option: Photodynamic treatment

Summary One large multicentre RCT found that photodynamic treatment with verteporfin reduced the risk of moderate and severe vision loss in selected people with exudative age related macular degeneration (those with predominantly classic lesions on fluorescein angiography).

Benefits

We found no systematic review. **Versus placebo:** We found one large multicentre double blind RCT of photodynamic treatment in 609 people with new and recurrent subfoveal choroidal neovascularisation due to age related macular degeneration. The intervention was a two stage procedure: infusion of verteporfin, followed by phototherapy with activating laser light. The control group received infusion of sugar water followed by phototherapy.[34] Twice as many participants were randomised to verteporfin. Treatments were repeated if necessary every three months. Outcomes were moderate and severe loss of visual acuity, defined as loss of 15 and 30 letters (about three and six lines) on a special eye chart, change in contrast sensitivity, and fluorescein angiographic appearance. At each follow up visit up to 12 months, all outcome measures were clinically and statistically significantly better in the treatment group than in the control group. At the 12 month follow up visit, 61% of treated people compared with 46% of controls had lost less than 15 letters of vision ($P<0.001$). Subgroup analysis found that this benefit was greater for eyes with predominantly classic choroidal neovascularisation lesions (67% treated *v* 39% control) and was most marked for eyes with pure classic lesions (77% treated *v* 27% control). However, no treatment benefit for visual acuity was seen in the group without predominantly classic lesions.

Harms

Verteporfin is a photosensitive dye, and care must be taken to avoid tissue extravasation during infusion and exposure to bright sunlight for 24 hours after treatment. The treatment was well tolerated but was more likely than the control intervention to cause a transient decrease in vision (18% treated *v* 12% control), injection site reactions (13% treated *v* 3% control), photosensitivity (3% treated *v* 0%

Glossary

Age related maculopathy Degenerative disease of the macula (centre of the retina) classified as early (marked by drusen and pigmentary change, and usually associated with normal vision) and late, when it is known as age related macular degeneration

Choroidal neovascularisation New vessels in the choroid, classified on the basis of fluorescein angiography: in terms of its position in relation to the fovea—extrafoveal, juxtafoveal, or subfoveal; in terms of its appearance—classic (well defined) or occult (poorly defined); and in terms of its borders—well demarcated or poorly demarcated.

Legal blindness Visual acuity $< 20/200$.

Photodynamic treatment A two step procedure of intravenous infusion of a photosensitive dye followed by application of a non-thermal laser which activates the dye. The treatment aims to cause selective closure of the choroidal new vessels.

Submacular surgery Removal of haemorrhage or choroidal neovascularisation, or both, after vitrectomy.

Verteporfin A photosensitive dye used in photodynamic treatment.

control), and low back pain related to infusion (2% *v* 0% control).

Comment

The RCT is ongoing and will report outcomes at 24 months' follow up. A further multicentre double blind RCT is under way comparing photodynamic treatment with verteporfin in a wider range of people with exudative age related macular degeneration (VIP Study Group, personal communication). Photodynamic treatment with other photosensitising dyes is also being evaluated in RCTs.

Competing interests: JA was a clinical investigator in the study of photodynamic treatment using verteporfin, which was funded by CIBA Vision/QLT. She has been supported by CIBA Vision for attendance at conferences and symposia.

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Endpiece

Out of health

A hypochrondiac, who had been to several doctors of eminence and was dissatisfied with them all, came to 74 Brook Street, and after a brief examination begged to know the result. "Sir," said Dr Gull, "you are a healthy man who is out of health." "Yes," said the patient, "that's exactly it; but why didn't the other doctors find it out?"

In memoriam: Sir William Gull. *Guy's Hosp Rep* 1980;47:xxv-xliii.

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