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Br. J. Ophthalmol. 2006;90;1188-1196
doi:10.1136/bjo.2005.082255

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PERSPECTIVE

Evolving European guidance on the medical management of neovascular age related macular degeneration

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Background: Until recently, only two options were available for the treatment of choroidal neovascularisation (CNV) associated with age related macular degeneration (AMD)—thermal laser photocoagulation and photodynamic therapy with verteporfin (PDT-V). However, new treatments for CNV are in development, and data from phase III clinical trials of some of these pharmacological interventions are now available. In light of these new data, expert guidance is required to enable retina specialists with expertise in the management of AMD to select and use the most appropriate therapies for the treatment of neovascular AMD.

Methods: Consensus from a round table of European retina specialists was obtained based on best available scientific data. Data rated at evidence levels 1 and 2 were evaluated for laser photocoagulation, PDT-V, pegaptanib sodium, and ranibizumab. Other treatments discussed are anecortave acetate, triamcinolone acetonide, bevacizumab, rostoporfin (SnET2), squalamine, and transpupillary thermotherapy.

Results: PDT-V is currently recommended for subfoveal lesions with predominantly classic CNV, or with occult with no classic CNV with evidence of recent disease progression and a lesion size ≤ 4 Macular Photocoagulation Study (MPS) disc areas (DA). The new classes of anti-angiogenic agents—namely, pegaptanib sodium and ranibizumab (the latter when peer reviewed phase III data become available) are recommended for subfoveal lesions with any proportion of classic CNV or occult with no classic CNV. For juxtafoveal classic CNV, PDT-V or anti-angiogenic therapy should be considered if the new vessels are so close to the fovea that laser photocoagulation would almost certainly extend under the centre of the foveal avascular zone. For all other well demarcated juxtafoveal lesions and for extrafoveal classic lesions, laser photocoagulation remains the standard treatment. Therapy should be undertaken within 1 week of the fluorescein angiogram on which the clinical decision to treat is based. At each follow up, fluorescein angiography should be performed and best corrected visual acuity measured as a minimum requirement.

Conclusions: These recommendations provide evidence based guidance for the choice and use of non-surgical therapies for the management of neovascular AMD. Revisions of the recommendations may be required as new data become available.

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Accepted for publication
19 May 2006

Early detection, diagnosis, and treatment of choroidal neovascularisation (CNV) is essential to maximise the preservation of central vision, minimise the risk of blindness, and protect the patient's quality of life.¹ Guidelines for the management of CNV associated with age related macular degeneration (AMD) based on clinical trial data and expert opinion have been published.^{2,3} However, a wealth of information on a number of new treatments has recently become available. A roundtable discussion group of European retina specialists was held to discuss and interpret data from ongoing phase III clinical trials and new phase II studies, and to evaluate the impact of the new data on the management of neovascular AMD in Europe. The meeting objective was to reach a consensus based on the best available evidence and to provide guidance to enable retina specialists to select and use the most appropriate therapies in the treatment of neovascular AMD.

Therapies for the treatment of neovascular AMD evaluated by the round table were thermal laser photocoagulation; photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Pharma AG); pegaptanib sodium (Macugen, Eyetech Pharmaceuticals, Inc/Pfizer Inc); ranibizumab (Lucentis, Genentech, Inc/Novartis Pharma AG); and anecortave acetate (Retaane, Alcon, Inc). It is impossible to directly compare results across these studies because of

different baseline vision characteristics. However, in the absence of head to head comparative trials, treatment decisions must be made through assessments of the results of different studies, and the brief overview of studies given below may prove useful for such evaluations. It was agreed that only data from randomised controlled clinical trials (that is, level 1 and 2 evidence; table 1) should be considered when making recommendations for initiating treatment. However, the panel agreed that data from post-marketing surveillance studies and clinical experience should be used to inform decision making regarding cessation of therapy. Where data are scarce no recommendation has been made with regard to specific therapies. Consensus was also sought regarding the use of transpupillary thermotherapy (TTT; Iridex Corporation), PDT with rostoporfin (SnET2; Photrex, Miravant Medical Technologies), systemic squalamine

Abbreviations: AMD, age related macular degeneration; CNV, choroidal neovascularisation; DA, disc areas; EMEA, European Agency for the Evaluation of Medical Products; FDA, Food and Drug Administration; ICG, indocyanine green; IVTA, intravitreal TA; MPS, Macular Photocoagulation Study; OCT, optical coherence tomography; PDT, photodynamic therapy; PDT-V, photocoagulation and photodynamic therapy with verteporfin; RPE, retinal pigment epithelium; TA, triamcinolone acetonide; TTT, transpupillary thermotherapy; VEGF, vascular endothelial growth factor

Table 1 Levels of evidence assigned to scientific data

Level of evidence	Description
1	Randomised clinical trial with low study errors or a meta-analysis
2	Randomised clinical trial with high study error; usually "underpowered"
3	Clinical trial including a control group, with non-random treatment allocation
4	Interventional case series
5	Interventional case report

therapy (Evizon, Genaera Corporation), intravitreally administered triamcinolone acetate (TA; Kenalog, Bristol-Myers Squibb Company), and intravitreally administered bevacizumab (Avastin, Genentech, Inc).

Revisions to these recommendations may be required as new data become available.

ASSESSING THE EVIDENCE FOR ESTABLISHED TREATMENTS

Laser photocoagulation

The objective of thermal laser photocoagulation is to occlude leaking blood vessels in CNV using a laser beam. This ameliorates the marked reduction in visual acuity resulting from the natural history of the disease.^{4,5} This was elegantly demonstrated in the Macular Photocoagulation Studies (MPS), a series of multicentre, randomised, controlled clinical trials performed in the 1980s, which investigated laser photocoagulation of CNV in patients with AMD, presumed ocular histoplasmosis syndrome, or idiopathic causes.⁶ However, thermal laser photocoagulation is considered to be effective only in eyes with selective angiographic characteristics.^{7,8} Furthermore, persistent or recurrent CNV occurs in approximately 50% of thermal laser treated eyes within 3 years of therapy.⁹ In addition, significant and immediate vision loss is common after thermal laser for subfoveal CNV, as a result of damage to the overlying retinal tissue.⁸ Therefore, thermal laser is currently only recommended for the treatment of extrafoveal lesions and juxtafoveal CNV in which the treatment scar would *not* extend under the centre of the foveal avascular zone.

Photodynamic therapy with verteporfin (PDT-V)

Verteporfin (Visudyne, Novartis Pharma AG) was the first pharmacological therapy approved for the treatment of subfoveal CNV as a result of AMD. PDT-V is a two step process involving the intravenous administration of verteporfin—a drug that predominantly accumulates within the endothelial cells of blood vessels—and subsequent activation of this drug by light at a wavelength of 689 nm, delivered using a non-thermal laser. Photoactivation of the drug generates short lived reactive oxygen species that cause

Trials and studies

ETDRS, Early Treatment of Diabetic Retinopathy Study; FOCUS, RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety; MPS, Macular Photocoagulation Study; TAP Investigation, Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Investigation; VIM Trial, Visudyne in Minimally Classic AMD Trial; VIP Trial, Verteporfin In Photodynamic Therapy Trial; VISION, VEGF Inhibition Study In Ocular Neovascularisation trials

localised damage to the CNV endothelial cells, leading to platelet aggregation and occlusion of the CNV with minimal damage to the overlying retina.

PDT-V, administered every 3 months, was shown to be both safe and effective in the phase III randomised, controlled, double masked Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Investigation, which comprised two trials. Because the study protocols for the two trials were identical and ran concurrently, and since the baseline characteristics, completeness of follow up, and outcomes were similar in both trials, combined results were analysed and reported.¹⁰ In the combined analysis PDT-V was seen to reduce the risk of moderate (decrease of three or more lines) and severe (decrease of six or more lines) visual acuity loss.¹⁰ The visual acuity benefits of PDT-V were greatest in the subgroup of eyes classified by fluorescein angiography at baseline as harbouring predominantly classic CNV (table 2), with 59% of 159 verteporfin treated eyes losing less than three lines of visual acuity through 2 years, compared with 31% of 83 placebo recipients ($p < 0.001$).¹⁰ The beneficial effects of PDT-V treatment were shown to be maintained through 5 years in the open label extension of the TAP investigation.^a The number of treatments required decreased from an average of 3.4 in the first year of the TAP investigation to 2.2 in the second year, and to 0.4 by the fourth year in the open label extension.^a

PDT-V was also found to be beneficial for eyes with recent progression of occult with no classic CNV in the phase III randomised, controlled, double masked Verteporfin In Photodynamic Therapy (VIP) Trial at 2 years (table 3).¹¹ Retrospective subgroup analyses showed that a greater proportion of eyes with either smaller lesions (≤ 4 MPS disc areas (DA)) or lower levels of visual acuity (worse than 20/50) lost fewer than three lines of visual acuity compared with placebo recipients (54% v 39%, respectively, at 1 year, 51% v 25% at 2 years; $p < 0.001$).

Additional subgroup analysis of the TAP study data suggested a benefit for eyes with minimally classic CNV that either had small lesions (< 4 MPS DA) or lower levels of visual acuity (≤ 65 letters). In this subgroup, 58% of 57 treated eyes lost fewer than three lines of visual acuity at

Table 2 Outcomes by therapy in predominantly classic CNV

Therapy	Trial	No of treated eyes	No of placebo eyes	Proportion of eyes with < 3 lines of visual acuity loss
PDT-V	TAP Investigation ¹⁰	159	83	At 1 year: 67% treated v 40% placebo ($p < 0.001$) At 2 years: 59% treated v 31% placebo ($p < 0.001$)
Pegaptanib sodium	EOP1003 and 1004*	74	79	At 1 year: 68% treated (0.3 mg) v 57.5% placebo
Anecortave acetate (AA)	C-98-03 ¹⁷	25	26	At 1 year: 84% treated (15 mg) v 50% placebo ($p = 0.01$)

*These data have not been published—values estimated from data on file at the FDA: http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4053B1_02_FDA-Backgrounder.pdf.

Table 3 Outcomes by therapy in occult with no classic CNV

Therapy	Trial	No of treated eyes	No of placebo eyes	Proportion of eyes with <3 lines of visual acuity loss
PDT-V	VIP Trial ¹¹	166	92	At 1 year: 49% treated v 45% placebo At 2 years: 45% treated v 32% placebo (p=0.032)
Pegaptanib sodium	EOP1003 and 1004*	115	124	At 1 year: 66% treated (0.3 mg) v 64.5% placebo

*These data have not been published—values estimated from data on file at the FDA: http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4053B1_02_FDA-Background.pdf.

1 year, compared with 37% of 27 placebo recipients.^b These findings provided the rationale for the Visudyne in Minimally Classic (VIM) AMD Trial, a phase II study of 117 eyes with minimally classic lesions (<6 MPS DA), which were randomised to one of three arms: placebo, PDT-V with standard fluence, or PDT-V with reduced laser fluence (table 4). At 2 years, fewer treated eyes (5% of the reduced fluence group and 3% of the standard fluence group) developed predominantly classic CNV, compared with 28% of placebo eyes (p<0.01).¹²

Retrospective, detailed, exploratory analyses of the combined TAP and VIP data suggest that lesion size may be an important predictor for treatment outcome after PDT-V, as it may correspond to different stages of lesion evolution.¹³ The only clinically relevant ocular adverse event observed in studies with PDT-V was acute severe visual acuity decrease (loss of more than four lines of visual acuity within 7 days of PDT-V therapy), which occurred in three (0.7%) of 402 patients in the TAP Investigation and 10 (4.4%) of 225 patients in the VIP Trial.¹⁴ In Europe, PDT-V is approved for the treatment of subfoveal lesions composed of predominantly classic CNV, and for occult lesions with no classic CNV with evidence of recent disease progression.

Pegaptanib sodium

Pegaptanib sodium (Macugen, Eyetech/Pfizer) is a pegylated oligonucleotide that specifically binds to isoform 165 of vascular endothelial growth factor (VEGF), thereby partially inhibiting VEGF induced increases in vascular permeability and neovascularisation. It is administered every 6 weeks by intravitreal injection (that is, nine times per year) for at least 2 years.

Pegaptanib sodium has been evaluated in a total of 1186 eyes (randomised 1:1:1:1 to three different doses and sham) in two phase II/III randomised, controlled, double masked studies collectively known as the VEGF Inhibition Study In Ocular Neovascularisation (VISION) trials, one study being performed in the United States and Canada and the other at sites in other developed countries (tables 2–4).¹⁵ In a combined analysis of the primary end point (loss of <15 letters of visual acuity from baseline), the 0.3 mg dose of pegaptanib sodium demonstrated efficacy at 2 years.^c The treatment was efficacious across all CNV subtypes, with the

categorisation assignment based on the pre-randomisation fluorescein angiogram. The treatment effect was also more pronounced for small (≤ 4 MPS DA) lesions.¹⁵ Fluorescein angiography, which was performed at baseline and at weeks 30 and 54, was not used as a guide for re-treatment, but a reduced growth in lesion size in treated eyes relative to the placebo group was documented.¹⁵ In subgroup analyses of the replicate trials, similar outcomes were present only in eyes with minimally classic lesions.^{d e} This may reflect the lack of power to detect differences in outcome parameters in other lesion types because of the small numbers in the different subgroups. It should also be noted that concomitant use of PDT-V was permitted for eyes with predominantly classic CNV. The majority of the eyes in this subgroup, particularly those in the US trial, received PDT-V, making it difficult to assess the efficacy of pegaptanib sodium independently of PDT-V in eyes with predominantly classic CNV.

Injection related complications included endophthalmitis, retinal detachment and traumatic cataract.¹⁵ However, following a protocol amendment, the risk of endophthalmitis was markedly reduced (<0.2%). All but one of the cases of endophthalmitis were successfully managed without additional vision loss, and three quarters of the patients with endophthalmitis remained in the trial. Therefore, the risk of endophthalmitis associated with the use of pegaptanib sodium was considered acceptable by the panel, especially when compared with the risk of no treatment.

The VISION trials provided proof of concept for VEGF inhibition in CNV caused by AMD. However, several questions regarding the treatment protocol remain unanswered, including the most appropriate markers for re-treatment (that is, visual acuity alone, or fluorescein or indocyanine green (ICG) angiography or optical coherence tomography (OCT)); the optimal treatment interval (6 weeks or another interval); and the length of time that the patient should remain on treatment (1–2 years or more). Despite these caveats, pegaptanib sodium is recommended where PDT-V is of little or no benefit. There are currently no studies directly comparing pegaptanib sodium and PDT-V. Approval of pegaptanib sodium for the treatment of all AMD lesion types has been granted by the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medical Products (EMEA).

Table 4 Outcomes by therapy in minimally classic CNV

Therapy	Trial	No of treated eyes	No of placebo eyes	Proportion of eyes with <3 lines of visual acuity loss
PDT-V	TAP Investigation ¹⁰ VIM Trial ¹²	202 77	104 40	At 2 years: 48% treated v 44% placebo (p=0.58) At 1 year: 86% (reduced fluence regimen) and 72% (standard regimen) v 53% placebo (combined PDT-V groups p<0.01) At 2 years: 74% (reduced fluence regimen) and 47% (standard regimen) v 38% placebo (combined PDT-V groups p=0.03)
Pegaptanib sodium	EOP1003 and 1004*	113	104	At 1 year: 76.5% treated (0.3 mg) v 54.5% placebo

*These data have not been published—values estimated from data on file at the FDA: http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4053B1_02_FDA-Background.pdf.

Ranibizumab

Ranibizumab (Lucentis, Genentech/Novartis) is a humanised, recombinant monoclonal antibody fragment designed to recognise all five human isoforms of VEGF. In animal studies, it has been shown to penetrate through all retinal layers and inhibit VEGF-A, thereby decreasing vascular permeability and blocking angiogenesis.¹⁶ Ranibizumab is delivered by monthly intravitreal injection. In a phase I/II trial in 64 eyes, an improvement in visual acuity (assessed with Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity charts) after treatment with ranibizumab was associated with reduction of intraretinal and subretinal fluid on OCT, and inhibition of neovascular growth and leakage in a range of lesion types was demonstrated on fluorescein angiography.^f Results from the phase III trial, MARINA, which enrolled 716 patients with minimally classic or occult CNV in multiple clinical sites in the United States showed that 95% of eyes treated with ranibizumab had maintained or improved visual acuity (loss of <15 letters) at 1 year, compared with 62% of eyes in the sham injection group ($p = 0.0001$).^g The results at 2 years seem to be maintained. In a second phase III trial, ANCHOR, which enrolled 426 patients with predominantly classic CNV, 94% and 96% of eyes treated with 0.3 mg or 0.5 mg of ranibizumab, respectively, lost fewer than three lines of acuity at 1 year, compared to 64% of PDT-V treated eyes. In addition, a gain of 15 or more letters occurred in 35.7%, 40.3% of eyes that received 0.3 mg or 0.5 mg of ranibizumab compared with 5.6% of PDT-V treated eyes. An ongoing phase IIIb study, PIER, is evaluating a less frequent dosing regimen which seems less effective than the 4 weekly regimen used in the ANCHOR and MARINA trials.

Preliminary results from a randomised phase I/II trial, RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety (FOCUS), have also recently been released.^h In this trial, the benefit of ranibizumab in combination with PDT-V versus PDT-V alone was investigated in 162 eyes with predominantly classic CNV. Approximately 90% of eyes treated with the combination of ranibizumab and PDT-V demonstrated maintained or improved visual acuity compared with 68% of those treated with PDT-V alone.^h Furthermore, it was reported that eyes treated with the combination of ranibizumab and PDT-V had a significant improvement in visual acuity compared with visual acuity at study entry, whereas the PDT-V only group demonstrated a decrease in mean visual acuity from baseline at 12 months.^h

A preliminary analysis of the safety data from the phase I/II FOCUS trial identified an increased risk of uveitis in patients treated with ranibizumab and PDT-V, compared with patients treated with PDT-V alone.^h Therefore, the study protocol was amended to induce immunological tolerance—patients received the lowest dose at study entry, which was then increased progressively over time. After uveitis, endophthalmitis was the next most common ocular serious adverse event. The incidence of non-ocular serious adverse events (cerebral vascular events and myocardial infarctions) varied slightly between the two treatment arms but was not statistically significant. In an analysis of long term safety data from 70 patients enrolled in an open label extension to the phase I/II studies, the most common adverse events of the study eye were conjunctival haemorrhage, eye pain, blurred vision, iris and uveal tract inflammations, and increased intraocular pressure; these events were mild or moderate in severity. The most common non-ocular adverse events were mild nasopharyngitis, and a small increase in blood pressure.ⁱ The frequency and nature of the adverse events in the MARINA trial were similar to those seen in earlier trials.^g Intravitreal ranibizumab therapy is likely to become the standard of care, but published peer reviewed data are

needed before any strong recommendation for its use can be given.

Anecortave acetate

Anecortave acetate (Retaane, Alcon) is an angiostatic cortisone that has been designed to block the migration of proliferating endothelial cells by inhibiting metalloproteinases. Anecortave acetate is devoid of conventional steroidal pharmacological properties, such as increased intraocular pressure and progression of cataract. It is administered every 6 months by posterior juxtasclear delivery.

Promising results were seen in a phase II dose-response study investigating the safety and efficacy of anecortave acetate monotherapy in 128 eyes with subfoveal CNV¹⁷ (table 2). A statistically significant visual acuity benefit was observed in the treatment arm compared with the placebo arm. However, there was a relatively high discontinuation rate: 41% of patients withdrew from the study before month 12, with the majority (26%) leaving because of disease progression, and 15% because of adverse events.¹⁷ This level of loss of participants raises concerns, and the results of the study must be viewed with caution.

Data from a phase III randomised, double masked study comparing anecortave acetate and PDT-V showed that the former failed to achieve non-inferiority to PDT-V at 12 months, with 45% of anecortave treated eyes losing fewer than three lines compared with 49% of verteporfin treated eyes ($p = 0.43$).¹⁸ The investigators suggest that reflux of the study medication through the conjunctival incision site; and non-adherence to the specified re-treatment interval, leading to longer and less optimal intervals between injections could have negatively impacted on study outcomes. For eyes that were treated within 6 months and that experienced no reflux, 57% (of 75) lost fewer than three lines of visual acuity.¹⁸ To address these factors, the drug administration procedure has been modified to include a counter pressure device to minimise reflux, and a pharmacokinetic study to evaluate the effect of this device is in progress. In an analysis of safety data from 883 patients, anecortave acetate was shown to be well tolerated, with an excellent safety profile.¹

It has been suggested that a transient inflammatory response may be initiated by treatment with PDT¹⁹; thus, combination therapy with anti-inflammatory agents such as steroids might be expected to enhance treatment outcomes. A 6 month phase II combination study anecortave acetate and PDT-V compared with PDT-V in 136 eyes with classic CNV suggested a trend towards greater efficacy with the combination (78% v 67%, experiencing three lines of visual acuity loss), although this difference did not achieve statistical significance in the short follow up period.^m

Triamcinolone acetonide

Steroids have both direct and indirect effects on angiogenesis, vascular permeability, and inflammation.²⁰ In vitro, steroids inhibit VEGF expression, degrade the CNV basement membrane and downregulate the expression of ICAM-1 and extracellular matrix metalloproteinases.²⁰ Triamcinolone acetonide (TA, Kenalog, Bristol-Myers Squibb) has fivefold greater anti-inflammatory activity than hydrocortisone, and a longer duration of action than other steroids. While it does not carry a label for intraocular use, several small trials have examined the effects of intravitreal TA (IVTA) on subfoveal lesions.^{21–24} Currently, there are no data that support the use of TA as monotherapy for the treatment of CNV as a result of AMD, and, therefore, its use is not recommended.

IVTA is widely used in both the United States and Europe as an adjunct to PDT-V. Data are currently restricted to those obtained from the lowest level of evidence—namely, results from ad hoc case series (table 5). The results of such studies,

Table 5 Outcomes of intravitreal triamcinolone acetonide and PDT-V in eyes with CNV

Reference	No of eyes	Lesion type	TA dose	Follow up (months)	Outcome
Rechtman 2004 ²³	14	Classic and/or occult	4 mg	12-25	Visual acuity improvement in 7% and stabilisation in 50%. Adverse events: intraocular pressure elevation in 29%, cataract progression in 50% of phakic eyes. Number of re-treatments during the first year was 2.6 VA stabilisation in 81% of eyes and improvement of ≥ 2 lines in 21%. In 13 patients without previous treatment: mean improvement of 2.4 lines at 6 months. In 13 patients who had at least one previous PDT-V: no significant difference between visual acuity at baseline compared with 6 months. No eye in either group lost three or more lines. Five (19.2%) eyes required topical therapy to control intraocular pressure
Roth 2004 ^v	72	Subfoveal	4 mg	6	
Spaide 2003 ²²	26	All types	4 mg	6	

while indicative of a promising effect when PDT-V and IVTA are combined, should be treated with caution. The panel agreed that administration of IVTA is not recommended until the results of the ongoing randomised, controlled studies of PDT-V and adjunctive IVTA are made available (five trials, ranging in size from 100 to 300 patients, are currently under way). In particular, factors such as the optimum dose and the timing of administration of the adjuvant IVTA need to be determined. Further information is also required on the risk of adverse effects, such as increased intraocular pressure, endophthalmitis, and development of cataract. Intracameral administration of TA is not recommended. It is worth noting that, for all drugs administered via intraocular routes, recently published guidelines from a consensus meeting describe strategies for the delivery of intravitreal injections that reduce risks and improve outcomes.²⁵

It is also possible that a combination of agents with anti-permeability and anti-angiogenic effects may provide a synergistic effect, and a trial is under way to evaluate the combination of anecortave acetate and triamcinolone acetonide versus the use of each agent alone in eyes with occult or minimally classic subfoveal CNV.¹¹ At the present time, there is insufficient evidence of efficacy to recommend the use of anecortave acetate in the treatment of neovascular AMD.

Rostaporfin

Rostaporfin (SnET2, Photrex, Miravant), like verteporfin, is a light activated, cytotoxic drug used in PDT. Preliminary results from two phase III trials involving 920 eyes with subfoveal CNV <3 mm in size were reported at congresses in 2004. At 2 years, 58% of 231 rostoporfin treated eyes lost fewer than three lines of visual acuity, compared with 42% of 119 eyes given placebo.⁹ The greatest benefit was seen for eyes with occult CNV occupying >50% of the area of the lesion: 65% of eyes lost fewer than three lines of visual acuity, compared with 29% of placebo eyes (table 3).⁹ Subgroup analyses also demonstrated that eyes with better baseline visual acuity (>45 letters) had the greatest visual acuity benefit.⁹ Rostaporfin was well tolerated, with a good safety profile.⁷ No recommendations can be made for the use of rostoporfin until further data from a confirmation trial become available.

Transpupillary thermotherapy

Transpupillary thermotherapy (TTT, Iridex) uses a low (810 nm) dose of infrared laser light, without adjunctive pharmacological therapies, to treat eyes with neovascular AMD. Preliminary results from a phase III trial in 303 eyes with occult CNV showed that TTT did not result in a significant benefit relative to placebo.¹¹ Current evidence does not support the use of TTT, and the panel thought that it could not recommend its use in the management of neovascular AMD.

Agents that have not been tested in phase III studies

Bevacizumab (Avastin, Genentech, Inc) is a humanised monoclonal antibody to VEGF designed for intravenous administration and approved for the treatment of colorectal cancer.²⁶ It is derived from the same murine anti-VEGF antibody as ranibizumab. The promising results with bevacizumab have raised the expectations of the retina specialist as well as of the patients. Ranibizumab is expected to be licensed as an intravitreal treatment for exudative AMD by the FDA and the European Union within the next year. Although bevacizumab has a licence for the treatment of colorectal cancer it is not licensed for the treatment of AMD and is therefore available for use on an off-label basis. Following the publication of highly encouraging data²⁷⁻²⁸ many investigators worldwide are exploring the use of intravitreal Bevacizumab with several reports on short term safety and efficacy available in the literature.²⁹⁻³⁷ Also experimental and electrophysiological testing in animals and humans demonstrate absence of toxicity to the retina.³⁸⁻³⁹

In spite of promising short term results reported this panel agreed that administration of intravitreal bevacizumab can not be formally recommended until results of a randomised clinical trial are available. No randomised clinical trial is at present planned to evaluate efficacy of intravitreal bevacizumab.

This panel decided not to make any positive or negative recommendation for the use of intravitreal bevacizumab with the current information.

Squalamine

Squalamine (Genaera Corporation) is an intravenously administered aminosterol with anti-angiogenic properties. It blocks growth factor signalling within endothelial cells by inhibition of VEGF and integrin expression. In addition, it blocks endothelial cytoskeletal formation. These effects result in endothelial-cell inactivation and apoptosis. In a prospective phase I/II study in 40 eyes with classic, occult, and mixed choroidal neovascular lesions, intravenous administration every 4 weeks resulted in at least a three line improvement in 10 eyes (26%) at the 4 month visit, while visual acuity remained stable in 29 eyes (74%).⁵ Squalamine has been shown to inhibit new vessel formation without significant regression of existing lesions, and, depending on the lesion composition, combination with adjunctive therapies may be appropriate. Squalamine is currently being investigated in three phase II trials, one of which is evaluating squalamine in combination with PDT-V.¹ Until level 1 or 2 evidence becomes available, no recommendations can be made for the use of squalamine in the treatment of CNV caused by AMD.

DIAGNOSIS

Fluorescein angiography is the minimum requirement on which to base any treatment decision in symptomatic eyes; stereo-fluorescein angiography provides clearer information. The panel agreed that OCT is helpful in the detection of

subretinal and intraretinal fluid (a characteristic that might be equivalent to the angiographic criterion of leakage), but OCT alone has not yet been demonstrated to be a sufficient diagnostic tool. ICG angiography may be useful if the diagnosis is uncertain and if subretinal blood hinders the detection of CNV using fluorescein angiography. Studies comparing the utility of ICG angiography with fluorescein angiography are currently under way, but until data are available and analysed, fluorescein angiography remains the diagnostic standard.

Therapy should be initiated within 1 week of the fluorescein angiogram on which the clinical decision to treat was based. Activity of the lesion is a prerequisite for all treatments. Before initiating therapy, the treating ophthalmologist should confirm with biomicroscopy that the lesion activity has not changed since the day of the diagnostic angiogram.

CHOICE OF THERAPY

Extrafoveal classic CNV

Thermal laser photocoagulation is indicated for extrafoveal classic lesions, after ruling out the presence of any associated occult CNV using ICG angiography. No treatment has been evaluated for predominantly or minimally classic extrafoveal lesions with evidence of occult CNV, or for occult with no classic extrafoveal CNV.

Juxtafoveal classic CNV

For juxtafoveal classic CNV, thermal laser photocoagulation is recommended. However, juxtafoveal classic CNV that is so close to the fovea that thermal laser photocoagulation would almost certainly extend under the centre of the foveal avascular zone or for predominantly or minimally classic juxtafoveal lesions with evidence of occult CNV, or for occult with no classic juxtafoveal CNV PDT-V or pegaptanib sodium are recommended. Following the issue of an FDA and EU licence and confirmation of phase III efficacy data ranibizumab is an additional first option therapy.

Subfoveal lesions

Predominantly classic CNV

PDT-V and pegaptanib sodium are recommended as monotherapies of choice to treat eyes that present with a subfoveal lesion composed of predominantly classic CNV, with or without evidence of (<50%) occult CNV.¹⁵ Following the issue of an FDA and EU licence and confirmation of phase III efficacy data ranibizumab is an additional first option therapy.

Minimally classic CNV

Presently, therapy with pegaptanib sodium is recommended for eyes with minimally classic subfoveal lesions of any size. PDT-V remains a possible option for the treatment of small (<4 MPS DA) minimally classic lesions. In lesions where the proportion of classic CNV is approximately 50%, it may be difficult to make a distinction between a minimally classic and a predominantly classic lesion, and the ophthalmologist may consider treatment with either therapy according to his or her clinical judgment. As previously stated once regulatory approval has been obtained and peer reviewed data become available ranibizumab is a first option therapy.

Occult with no classic CNV

Pegaptanib sodium is an option for occult with no classic CNV.¹⁵ However, for eyes with small (≤ 4 MPS DA) subfoveal occult with no classic CNV and presumed recent disease progression, or with visual acuity at a lower level (worse than 20/50), PDT-V may be considered.¹¹ Following the issue of an

FDA and EU licence and confirmation of phase III efficacy data ranibizumab is an additional first option therapy.

CNV and RPE detachment

There is currently no level 1 or 2 evidence available to recommend a particular therapy for the treatment of a vascularised retinal pigment epithelium (RPE) detachment.

TREATMENT ASSOCIATED ADVERSE EVENTS

Systemic adverse events associated with PDT-V were injection site reactions and infusion related back pain of varying severity.^{10 11} No systemic adverse events attributable to pegaptanib sodium were reported in the VISION trials.¹⁵

All adverse events attributable to thermal laser photocoagulation are ocular, and these include injury to the foveal retina, and tearing of the RPE.⁸ Severe post-treatment (within 7 days of therapy) loss of visual acuity is a recognised ocular adverse event following PDT-V. This occurred in three eyes in the TAP investigation (0.7%) and in 10 eyes in the VIP trial (4.4%).¹⁴ In the latter study, this occurred mainly in eyes with occult CNV (eight out of 10 eyes), those with large lesions (six out of 10 eyes), or those with good visual acuity (65 letters or better; seven out of 10 eyes). Intravitreal injections carry a risk of endophthalmitis, retinal detachment, and traumatic cataract. In the VISION trials, endophthalmitis occurred in <0.2% of eyes.¹⁵ Thus, both PDT-V and pegaptanib sodium appear to be safe and well tolerated.

FOLLOW UP OF TREATED EYES

Method of follow up

At each follow up examination, best corrected visual acuity measurements and fluorescein angiography should be performed as a minimum requirement. Techniques such as OCT and ICG angiography may prove to be of equal or greater diagnostic use, but this remains to be investigated in future studies. With all treatment options patients may need to return earlier if visual deterioration is noted between scheduled visits.

Thermal laser photocoagulation

Clinical and angiographic examinations should be performed at 2, 4, 8, and 12 weeks, although the patient should return earlier if new symptoms are experienced. Patients should receive re-treatment if there is angiographic evidence of continuing leakage from the CNV, unless this is precluded by the proximity of the lesion to the centre of the foveal avascular zone. The end point of laser photocoagulation is to obtain a flat atrophic scar without leakage at its borders on fluorescein angiography.

PDT-V

Patients should receive re-treatment as often as every 3 months if there is continuing fluorescein leakage from the CNV, if visual acuity loss has been documented, or if fluorescein angiography shows enlargement of the CNV compared with the previous angiogram. If fluorescein leakage is absent at a follow up examination (this is considered the end point for PDT-V therapy) re-treatment is not necessary and the follow up period may be extended. Visual acuity is not taken into consideration for decision making if fluorescein leakage is absent. These recommendations are in agreement with the existing guidelines for the use of PDT-V.^{2 3}

Pegaptanib sodium

Patients should receive re-treatment with pegaptanib sodium every 6 weeks, as recommended by the phase II/III study protocol.¹⁵ The end point and the duration of treatment with pegaptanib sodium are yet to be determined.

Failure to respond to therapy

There is currently no evidence on which to base guidelines on when it is appropriate to consider a treatment as failed, and whether an alternative form of treatment may be employed. The most common reason for a change in a therapy is the lack, or perceived lack, of efficacy of the treatment being used. A change in therapy is indicated following argon laser photocoagulation if recurrence involves the centre of the foveal avascular zone. A precise classification of the clinical features that identify the responders to PDT-V and pegaptanib sodium has not yet been performed. Conversely, failure to respond has never been defined in AMD clinical trials.

The following statements are opinions of the authors, and are based only on clinical experience:

- Failure to respond to thermal laser photocoagulation is suggested by angiographic evidence of persistent or recurrent CNV
- Failure to respond to PDT-V is suggested when a minimum of three sessions of PDT have been undertaken but there is continuing vision loss because of increasing cystoid change in the retina, recurrence or persistence of macular serous detachment, increasing or new haemorrhage, and/or increasing or new hard exudates
- Failure to respond to pegaptanib sodium is suggested by worsening vision despite three consecutive administrations of the agent. Morphologically, this should be accompanied by recurrence or persistence of macular serous detachment, new haemorrhage, and exudates. A similar algorithm may be applied to other anti-VEGF therapies as they become available.

The presence of these features associated with morphological worsening and a decrease in visual acuity is a valid reason to select another therapy. However, at this time, it is not known whether CNV that fails to respond to one treatment method will respond to another.

Combination of therapies

Theoretically, there may be a synergistic effect from combining therapies with different mechanisms of action. The combination of PDT-V with ranibizumab, squalamine, or triamcinolone acetonide is currently under investigation, and trials of pegaptanib sodium and anecortave acetate have included concurrent use of PDT-V (see relevant sections above). It is probable that improvement in vision could be achieved with double or even triple therapy regimens. However, until results from clinical trials are published, the use of combination therapies cannot be recommended.

Discontinuation of therapy

Discontinuation of treatment should be considered either if the end point is reached or if continuing treatment is judged unlikely to prevent further deterioration, and is thus unlikely to have a positive impact on the patient's quality of life.

Thermal laser photocoagulation

Treatment is not considered if no leakage from CNV is observed on fluorescein angiography or if CNV has progressed to involve the foveal avascular zone.

PDT-V

Re-treatment may be deferred if best corrected visual acuity is stable or improved, together with angiographic evidence of absence of CNV leakage. Reduction of visual acuity below 20/200 during follow up was not an indication for cessation of PDT-V in the clinical trials. All of the following fundus criteria should also be met: (i) there is minimal fluorescein leakage from CNV (<50% of the area treated at the previous

visit), without progression of fluorescein leakage beyond the boundaries of the area treated previously; (ii) the lesion has a scar-like appearance (fibrosis); (iii) there is minimal or no subretinal fluid on biomicroscopic examination and/or on OCT.² The patient should be reviewed every 3 months until re-treatment has been considered unnecessary for a period of 6 months. Thereafter, follow up may be scheduled at 6 month intervals, and, eventually, 12 month intervals.

Pegaptanib sodium

No data are available to produce guidelines for discontinuation of therapy with pegaptanib sodium, as the design of the study specified an intravitreal injection every 6 weeks for the duration of the 2 year trials. The present guidance will be updated as these data become available. The panel recommends that eyes which have received pegaptanib sodium are monitored regularly after cessation of therapy at 2 years.

Similar algorithms may be applied to other anti-angiogenic agents as these treatments become available.

CONCLUSIONS

The availability of new therapies has expanded the range of treatment options for CNV secondary to AMD. The results of the many randomised clinical trials suggest that the risk of severe visual acuity loss because of neovascular AMD may be delayed. With the introduction of the newer classes of anti-angiogenic agents, significant proportions of eyes will experience an improvement in visual acuity. Combination therapies are being developed to achieve optimal outcomes. The recommendations contained in this document provide

Glossary

Extrafoveal lesion—a lesion with the posterior margin located at least 200 µm from the geometric centre of the foveal avascular zone.

Juxtafoveal lesion—a lesion with the posterior margin located 1–199 µm from the centre of the foveal avascular zone.

Classic CNV—a fluorescent pattern on fluorescein angiography characterised by a well demarcated area of bright hyperfluorescence in the early phase, with fluorescein leakage through the mid and late phase frames, which obscures the boundaries of the lesion.

Predominantly classic CNV—an area of classic CNV occupying ≥50% of the area of the entire lesion at baseline.

Minimally classic CNV—an area of classic CNV occupying <50% but >0% of the area of the entire lesion at baseline.

Occult CNV—occult CNV is divided into two types based on the patterns observed on fluorescein angiography. Type 1 (vascularised pigment epithelial detachment) is characterised by irregular elevation of the retinal pigment epithelium, which appears as stippled hyperfluorescence, with boundaries that are often poorly demarcated, and fluorescein leakage into the late phase of the angiogram. Type 2 (late leakage of indeterminate origin) has poorly demarcated boundaries, with fluorescein leakage from an undetermined source in the late phase frames of the angiogram, which do not correspond to classic CNV or fibrovascular RPE detachment in the early or mid phase frames. ICG may disclose the vascular component of occult CNV, and give better delineation of the lesion boundaries.

Presumed recent disease progression—defined as the presence of blood from CNV, growth of the lesion (at least a 10% increase in the greatest linear dimension of the lesion), or deterioration of best corrected visual acuity (at least five letters or approximately one line) within the past 12 weeks.

guidance on the present choice and use of therapies in Europe. They are based on expert interpretation of data rated at evidence levels 1 and 2. The recommendations for re-treatment and cessation of treatment take into account recent published and unpublished evidence on established and emerging therapies. Revisions will be required as new data become available. Exceptional cases will always be encountered, and in such circumstances, treating ophthalmologists will need to use their own medical judgment and clinical experience.

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Competing interests: Usha Chakravarthy has been an investigator in the VISION study and has been a paid consultant in expert advisory boards for Novartis Pharma AG and Pfizer Inc. Gisèle Soubrane has participated in multiple expert advisory boards and has been reimbursed by Eyetech Pharmaceuticals, Inc, Novartis Pharma AG, Alcon, Inc, Pfizer Inc, Geniera Corporation and Allergan, Inc for attending several conferences and for running educational programmes. Francesco Bandello has been reimbursed by Novartis Pharma AG, Alcon, Inc, and Pfizer Inc for attending several conferences. Victor Chong has been reimbursed by Novartis Pharma AG for attending several conferences, and has received funds for a member of staff and fees for consultation. Catherine Creuzot-Garcher has declared no competing interests. Stavros A Dimitrakos has been reimbursed by Novartis Pharma AG for attending a meeting. Jean-François Korobelnik is a paid consultant for Pfizer Inc and has been paid by Alcon, Inc for running educational programmes. Michael Larsen has been reimbursed by Novartis Pharma AG and Pfizer Inc for speaking at symposia and for consulting services. Jordi Monés has participated in multiple expert advisory boards and has been reimbursed by Eyetech Pharmaceuticals, Inc, Novartis Pharma AG, Pfizer Inc, Allergan Inc, Geniera Corporation. Daniel Pauleikhoff has participated in multiple expert advisory boards and has been reimbursed by Pfizer Inc. Constantin J Pournaras has declared no competing interests. Giovanni Staurenghi has declared no competing interests. Gianni Virgili has been reimbursed by Novartis Pharma AG for attending several conferences and speaking at one conference. Sebastian Wolf has been reimbursed by Novartis Pharma AG, Pfizer Inc, and Alcon, Inc for attending several conferences, and has received research grants and consultancy fees from Novartis Pharma AG and Pfizer Inc.

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