Introduction

Neovascular age-related macular degeneration (AMD) is still one of the leading causes of substantial and irreversible vision loss. Because of the epidemiologic change in the age group affected by the disease — with a doubling of the proportion of individuals over 65 years of age anticipated by 2030 — the challenge for patients and physicians will increase. However, developments in therapeutic strategies have recently improved the efficacy of therapeutic interventions and increased the probability of patients avoiding vision loss or even gaining vision by an appropriate treatment.

With the broadening of the available armamentarium beyond laser therapy alone to a variety of pharmacological options, diagnostic and therapeutic paradigms are changing and indications are expanding. Accordingly, the strategies for clinical management need to be adapted to the use of novel modalities such as intravitreal administration of antiangiogenic substances.

ABSTRACT.

Neovascular age-related macular degeneration is becoming an increasing socio-medical problem as the proportion of the aged population is continuously increasing. However, new insights in the pathogenesis of the disease offer the opportunity to develop targeted therapies that attack the disease process more successfully than ever. This review article will focus on summarizing the actual options in the management of neovascular age-related macular degeneration and provide a short overview about recent therapeutic options in clinical and preclinical evaluation. The recent development of anti-VEGF substances for use in clinical routine has markedly improved the prognosis of patients with neovascular AMD. Intravitreal treatment with substances targeting all isotypes of vascular endothelial growth factor (VEGF), for the first time in the history of AMD treatments, results in a significant increase in visual acuity in patients with neovascular AMD. Overall, antiangiogenic approaches provide vision maintenance in over 90% and substantial improvement in 25–40% of patients. The combination with occlusive therapies like photodynamic therapy (PDT) potentially offers a reduction of re-treatment frequency and long-term maintenance of the treatment benefit. Further developments interacting with various steps in the angiogenic cascade are under clinical or preclinical evaluation and may soon become available. Nevertheless, the growing number of novel therapeutic options will have to provide proof of concept in randomized controlled clinical trials, a major challenge in view of the rapidly evolving field. For those therapies, which are already in clinical use, reasonable diagnostic tools for follow-up need to be developed, as the burden of continuous clinical monitoring of all patients and all indications is significant for patients and doctors. Ultimately, economic issues will be the limiting factor for the clinical availability of different treatment options.

Key words: age-related macular degeneration – choroidal neovascularization – guidelines – photocoagulation – photodynamic therapy – antiangiogenic therapy – combination therapy


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Perspectives

Guidance for the treatment of neovascular age-related macular degeneration

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The primary purpose of disease management is to minimize visual loss and related physical and emotional impairment and to optimize vision-related quality of life. With novel insight into the benefit and risks of established and emerging strategies, a consensus regarding the clinical value of treatment developments is useful to provide appropriate and state-of-the-art guidance for the ophthalmological community. Treatment recommendations should be based on the outcome of prospective randomized clinical trials or, in the absence of such data, on the evaluation of all available clinical evidence supported by an interpretation by professionals in the field. A guidance paper can offer a base for decision making, but does not replace a comprehensive evaluation of the current knowledge and the specific circumstances of an individual patient. In addition, consensus guidance may assist the physician to identify a valuable treatment option in conditions where an application does not reflect a uniform community standard or an official approval by health authorities. In general, it is the physician’s responsibility to determine the medical appropriateness of a treatment strategy based on his or her professional knowledge, to recognize the patient’s needs and to obtain a complete informed consent in compliance with the legal conditions.

Scientifically valid and clinically meaningful information should be based on a high level of evidence. The strongest evidence of level I is provided by results from at least one randomized, controlled clinical trial or a meta-analysis of several randomized controlled trials. Level II includes evidence from controlled trials without randomization and analysis of well-designed cohort or case-control studies preferably from multiple centres or multiple time series. Level III is based on descriptive studies, case reports or published expert opinion (AAO 2006).

Treatment strategies in neovascular AMD

**Photocoagulation**

**Principle**

A laser is used to thermally ablate a neovascular membrane. Due to collateral damage to adjacent neurosensory retina, an absolute scotoma occurs at the treated site. The purpose of this type of destructive treatment is to halt disease progression. In extrafoveal lesions, coagulation has been shown to be effective in maintaining central vision in a selected population. In subfoveal choroidal neovascularization (CNV), photocoagulation may induce iatrogenic vision loss, but limit the size of the central field defect on long-term follow-up.

**Evidence**

The Macula Photocoagulation study (MPS) has evaluated the efficacy and durability of thermal laser surgery in well-demarcated lesions with extra-, juxta- and subfoveal location and different lesion sizes (MPSG 1991, 1993, 1994).

Photocoagulation of extrafoveal CNV led to an important improvement in visual prognosis and a significant reduction of progressive vision loss for the initial 2 years. The relative risk of severe visual loss of 6 or more lines among untreated eyes compared with treated eyes was 1.5 from 6 months through 5 years. During long-term follow-up, a recurrence rate of 54% reduced the primary benefit, particularly since recurrent growth occurred to 90% at the border closest to the fovea (MPSG 1991). The benefit following coagulation of juxtafoveal CNV was limited by an even higher rate of persistence (i.e. leakage within 6 weeks of laser surgery) and recurrence (i.e. new leakage beyond 6 weeks of laser treatment). The rate of persistence or recurrence despite intervention was 80% over 5 years (MPSG 1994).

Photocoagulation of subfoveal CNV was primarily recommended for lesions smaller than two MPS disk areas with a substantial loss in visual acuity (VA) below 20/200. Eighty-two per cent of treated patients with subfoveal lesions ended up with a VA < 20/200 following primarily successful laser coagulation (MPSG 1993).

**Recommendation**

The high rate of recurrence should be considered, when performing laser coagulation in extra- and juxtafoveal lesions. However, in extrafoveal lesions severe vision loss of 6 or more lines is significantly lower in coagulated versus non-coagulated lesions.

Photocoagulation may be a practical option in eyes with extrafoveal recurrence of a large CNV, when the fovea demonstrates irreversible fibrotic or atrophic changes. Juxtafoveal lesions should not be treated with thermal coagulation, if the laser effect is likely to affect the foveal centre. Thermal laser ablation is not recommended as the first treatment choice for subfoveal lesions.

Recommendations are based on the MPS study data (evidence level I).

**Photodynamic therapy using verteporfin (visudyne)**

**Principle**

Photodynamic therapy (PDT) includes the intravenous administration of a pharmacological photosensitizer (e.g. verteporfin) combined with the physical activation of the substance using laser light in the red wavelength. Because the light is used to induce a photochemical oxidation of vascular endothelium, no thermal tissue damage occurs. In contrast to laser coagulation, retinal function is maintained and scotoma is not seen.

**Evidence**

In the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) study, subfoveal lesions up to 5400 μm in diameter and VA ranging from 20/40 to 20/200 were treated with verteporfin therapy (Bressler 2001). A benefit was found for the entire population, with 53% of the PDT-treated patients and 38% of the sham-treated patients losing fewer than 15 letters in VA at 2 years. Subgroup analysis revealed that the benefit was largest in predominantly classic lesions in which at least 50% of the entire lesion area is composed of a classic CNV component. In this lesion type, 59% of PDT-treated eyes compared with 31% of sham-treated eyes lost fewer than 15 letters (Table 1). No statistically significant difference was noted for minimally classic lesions in which the classic component represented less than 50% of the entire lesion area (Bressler 2001). Twenty-two per cent of eyes in the PDT group experienced a significant vision loss – defined as VA loss of more than 30 letters – compared to 36% in the sham group. An improvement in vision by 15 letters or more was seen in only 9% of treated patients at the 24 month visit (Table 2).
### Table 1. Stabilization of visual acuity ± 3 lines.

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Lesion type</th>
<th>Study</th>
<th>Control</th>
<th>Difference</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDT (quarterly, if lesion activity present)</td>
<td>Predom. classic CNV</td>
<td>59%</td>
<td>31%</td>
<td>28%</td>
<td>TAP / 24 months</td>
</tr>
<tr>
<td></td>
<td>Min. classic CNV</td>
<td>48%</td>
<td>44%</td>
<td>3%</td>
<td>TAP / 24 months</td>
</tr>
<tr>
<td></td>
<td>Occult CNV</td>
<td>45%</td>
<td>32%</td>
<td>13%</td>
<td>VIP / 24 months</td>
</tr>
<tr>
<td>Pegabtinib 0.3 mg (6 week intervals, fixed regimen)</td>
<td>All CNV subtypes</td>
<td>59%</td>
<td>45%</td>
<td>14%</td>
<td>VISION / 24 months</td>
</tr>
<tr>
<td></td>
<td>Predom. classic CNV</td>
<td>61%</td>
<td>42%</td>
<td>19%</td>
<td>VISION / 24 months</td>
</tr>
<tr>
<td></td>
<td>Min. classic CNV</td>
<td>61%</td>
<td>50%</td>
<td>11%</td>
<td>VISION / 24 months</td>
</tr>
<tr>
<td></td>
<td>Occult CNV</td>
<td>56%</td>
<td>41%</td>
<td>15%</td>
<td>VISION / 24 months</td>
</tr>
<tr>
<td>Ranibizumab 0.5 mg (4 week intervals, fixed regimen)</td>
<td>Predom. classic CNV</td>
<td>90%</td>
<td>66%</td>
<td>24%</td>
<td>ANCHOR / 24 months</td>
</tr>
<tr>
<td></td>
<td>Min. classic and occult CNV</td>
<td>90%</td>
<td>53%</td>
<td>37%</td>
<td>MARINA / 24 months</td>
</tr>
<tr>
<td></td>
<td>All CNV types</td>
<td>90%</td>
<td>49%</td>
<td>41%</td>
<td>PIER / 12 months</td>
</tr>
<tr>
<td>Combination PDT / ranibizumab (PDT quarterly, if needed; ranibizumab monthly, fixed regimen)</td>
<td>Predom. classic CNV</td>
<td>91%</td>
<td>68%</td>
<td>23%</td>
<td>FOCUS / 12 months</td>
</tr>
</tbody>
</table>

PDT: photodynamic therapy; CNV: choroidal neovascularization; TAP: treatment of age-related macular degeneration with photodynamic therapy; VIP: Verteporfin in Photodynamic Therapy study; VISION: VEGF Inhibition Study in Ocular Neovascularization; ANCHOR: Anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularization in age-related macular degeneration; MARINA: Minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of neovascular age-related macular degeneration; PIER: A phase IIIB multicenter, randomized, double-masked, sham injection controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal CNV with or without classic CNV secondary to age-related macular degeneration; FOCUS: A phase I/II, single-masked multicenter study of the safety, tolerability, and efficacy of multiple-dose intravitreal injections of rhuFab V2 in combination with verteporfin (visudyne) photodynamic therapy in subjects with neovascular age-related macular degeneration.

### Table 2. Improvement of ≥ 3 lines.

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Lesion type</th>
<th>Study</th>
<th>Control</th>
<th>Difference</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDT</td>
<td>Predom. classic and min. classic CNV</td>
<td>9%</td>
<td>4%</td>
<td>5%</td>
<td>TAP / 24 months</td>
</tr>
<tr>
<td></td>
<td>Occult CNV</td>
<td>5%</td>
<td>1%</td>
<td>4%</td>
<td>VIP / 24 months</td>
</tr>
<tr>
<td>Pegabtinib 0.3 mg</td>
<td>All CNV types</td>
<td>6%</td>
<td>2%</td>
<td>4%</td>
<td>VISION / 24 months</td>
</tr>
<tr>
<td>Ranibizumab 0.5 mg (3 monthly)</td>
<td>Predom. classic CNV</td>
<td>41%</td>
<td>6%</td>
<td>35%</td>
<td>ANCHOR / 24 months</td>
</tr>
<tr>
<td></td>
<td>Min. classic and occult CNV</td>
<td>35%</td>
<td>4%</td>
<td>29%</td>
<td>MARINA / 24 months</td>
</tr>
<tr>
<td>Ranibizumab 0.5 mg (3 monthly)</td>
<td>All CNV types</td>
<td>13%</td>
<td>10%</td>
<td>3%</td>
<td>PIER / 12 months</td>
</tr>
<tr>
<td>Combination PDT / ranibizumab</td>
<td>Predom. classic CNV</td>
<td>24%</td>
<td>5%</td>
<td>19%</td>
<td>FOCUS / 12 months</td>
</tr>
</tbody>
</table>

PDT: photodynamic therapy; CNV: choroidal neovascularization; TAP: treatment of age-related macular degeneration with photodynamic therapy; VIP: Verteporfin in Photodynamic Therapy study; VISION: VEGF Inhibition Study in Ocular Neovascularization; ANCHOR: Anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularization in age-related macular degeneration; MARINA: Minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of neovascular age-related macular degeneration; PIER: A phase IIIB multicenter, randomized, double-masked, sham injection controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal CNV with or without classic CNV secondary to age-related macular degeneration; FOCUS: A phase I/II, single-masked multicenter study of the safety, tolerability, and efficacy of multiple-dose intravitreal injections of rhuFab V2 in combination with verteporfin (visudyne) photodynamic therapy in subjects with neovascular age-related macular degeneration.

The Verteporfin in Photodynamic Therapy (VIP) study enrolled patients with subfoveal lesions composed of occult components without classic CNV (VIP Study Group 2001). Patients were only eligible if recent disease progression – including vision loss by at least 1 line, new haemorrhage or an enlargement of the CNV by at least 10%, as seen by angiography – was documented. At 2 years, 45% of PDT-treated eyes compared to 32% of sham-treated eyes lost less than 15 letters (Table 1). Subgroup analysis demonstrated that CNV with a lesion size < 4 MPS DA or worse initial VA < 65 letters had a better outcome: 51% of PDT-treated eyes lost less than 15 letters versus 25% in the placebo group. A significant loss of 30 letters or more was observed in 29% of eyes in the PDT group versus 47% in the placebo group.

In terms of general efficacy, the treatment is able to prevent further significant visual loss. The risk for a significant loss in vision is reduced to 50% compared to the spontaneous course of the disease (Pieramici et al. 2006). The mean visual loss ranges between 2 and 4 lines and the proportion of patients showing improvement following verteporfin therapy is very limited. At 24 months, an improvement of ≥ 1 to < 3 lines was seen in 8% and an increase of ≥ 3 to < 6 lines was seen in 5% of patients (VIP Study Group 2001) (Table 2).

Verteporfin therapy is a particularly safe treatment in terms of both systemic and ocular safety. Severe vision loss occurs rarely and is more often seen in the treatment of large occult lesions with a high initial VA (Arnold et al. 2004). In lesions with serous detachment of the retinal pigment epithelium (RPE), mechanical rips were observed. Even if an RPE rip does not
necessarily lead to further vision loss, lesions with a large exudative pigment epithelial detachment (PED) should not be treated with PDT monotherapy.

**Recommendation**
Verteporfin therapy is used as a standard therapy for neovascular AMD with predominantly classic CNV and occult CNV smaller than 4 MPS DA and recent disease progression. The advantage of the therapy is its safety and durability. The benefit or stabilization achieved during the first 2 years is usually maintained throughout 4 years, with few retreatments necessary after 2 years (TAP Study Group 2005). The mean treatment rate during the first year – 3.4 PDT courses – was relatively low. Considering the durability and relatively low effort, verteporfin therapy appears to be an appropriate alternative for patients unable to present continuously, a first eye with advanced disease and an unaffected fellow eye and a relatively small lesion. In general, lesion size was identified as the most important prognostic factor, with larger lesions presenting a less favourable outcome (Blinder et al. 2003).

Recommendations are based on the TAP and VIP study data (evidence level I).

**Combination of verteporfin therapy with intravitreal triamcinolone**

**Rationale**
Photodynamic effects are not selective for neovascular structures, but also affect physiological choroidal vessels (Schmidt-Erfurth et al. 2005). In particular, PDT induces an increased expression of vascular endothelial growth factor (VEGF) and inflammatory mediators (Schmidt-Erfurth et al. 2003). Steroids such as triamcinolone have an inhibiting effect on VEGF expression and inflammation. Intravitreal application of triamcinolone alone demonstrated a documented, but transient, reduction in CNV-related leakage (Gillies et al. 2003). Combination of verteporfin laser therapy and intravitreal triamcinolone may have an additive effect, improve vision outcome and reduce the rate of recurrence.

**Evidence**
In a small interventional case series, patients with CNV due to AMD had a visual benefit superior to a standard outcome following verteporfin monotherapy and required a lower number of retreatments compared to a historical control (Spaide et al. 2003). A large prospective, but non-controlled, series included 184 patients with all CNV types. VA improved in the majority of patients by a mean of 1.2 Snellen lines; the mean number of treatments required was 1.2 administrations (Augustin & Schmidt-Erfurth 2006). One year results of a randomized study in predominantly classic CNV demonstrated that at 12 month follow-up VA was significantly better in the group of patients who received combined therapy (Arias et al. 2006). Seventy-four per cent of patients treated with the combination lost fewer than 3 lines compared to 61% of patients treated with PDT monotherapy, and the retreatment rate was significantly lower. Use of a high dose of intravitreal triamcinolone at about 20 mg supported the results of a benefit with combination regarding final best corrected visual acuity (BCVA) and reduced need for retreatment compared to historical controls (Ruiz-Moreno et al. 2006). Several randomized clinical studies are underway to evaluate the benefit of combined verteporfin/triamcinolone therapy. Documented side-effects of intravitreal steroids are a progression in cataract formation – the reported frequency of eyes undergoing surgery ranges from 0% to 29% – and an increase in IOP, which may occur several months after administration, with a reported frequency of significant IOP elevation > 21 mmHg or requiring therapy ranging from 21% to 43%. Endophthalmitis is a rare event with intravitreal injections in general, but an increased incidence of sterile endophthalmitis or intraocular inflammation following intravitreal steroid injection has been described in the literature. The clinical appearance in these cases is complicated, because pain and swelling may be missing and the symptom onset may be delayed (Nelson et al. 2003).

**Recommendation**
Combination of verteporfin and intravitreal triamcinolone may be a useful alternative in patients who prefer a limited number of necessary treatments and the perspective of a relatively stable long-term situation. Whether corticosteroids should be considered as part of the standard care with photodynamic therapy depends on the outcome of ongoing controlled clinical trials (Zarbin 2006). The results from multiple large case series appear promising and the therapy is being used in clinical routine in many countries. The intravitreal intervention per se and the side-effects of steroids require controlled clinical care including screening for risk factors such as steroid response or glaucoma preoperatively and a careful postoperative follow-up to manage an inflammatory response or an increase of IOP appropriately. Based on ongoing trials using antiangiogenic adjuncts rather than steroids together with PDT, a standard combination may not include the off-label use of intravitreal steroids in the near future.

Recommendations are based on small prospective trials and larger interventional studies without randomization (evidence level II and III).

**Intravitreal pharmacotherapy using pegaptanib (macugen)**

**Rationale**
VEGF increases vascular permeability, enhances the inflammatory response and induces angiogenesis (Ferrara et al. 2003). The isoform VEGF 165 has been particularly implicated in blood–retinal barrier breakdown and pathological intraocular neovascularization. Pegaptanib sodium is an aptamer composed of ribonucleic acids; it competitively blocks VEGF 165 and may selectively inhibit pathological leakage and angiogenesis (Moshfeghi & Puliafito 2005). The substance has to be applied intravitreally, and reinjections have to be performed regularly as the molecule is degraded enzymatically by intraocular nucleases.

**Evidence**
Phase I studies demonstrated an impressive antiangiogenic effect with improvement by 3 lines in 26% of patients treated with monotherapy and in 60% of patients receiving a combination of verteporfin PDT and adjunctive pegaptanib injections (Gragoudas 2005). The VEGF Inhibition Study in Ocular Neovascularization (VISION) trial was designed as two double-masked, sham-controlled, dose-ranging studies including 0.3, 0.1 and 3.0 mg doses. A total of 1186 patients were included in the trial. All
subfoveal angiographic lesion types that covered less than 12 total disc areas and demonstrated at least 50% of CNV in the total lesion area were included. Evidence of recent disease progression with subretinal haemorrhage and/or lipid deposits and/or the loss of ≥ 3 lines in VA was required for minimally classic and occult-only lesions. PDT was permitted in patients with predominantly classic disease per US Food and Drug Administration (FDA)-approved label at the investigator’s discretion. The control group was offered usual care including PDT monotherapy. Intravitreal injections were performed regularly at 6 week intervals independent of the neovascular activity.

A dose of 0.3 mg pegabtanib was identified as the optimal dosage. At 54 weeks, 70% versus 55% of eyes achieved the primary endpoint of losing < 15 letters of vision and 6% versus 2% of eyes gained ≥ 15 letters (Gragoudas et al. 2004). Pegabtanib patients lost a mean of 9 letters over 1 year compared to a loss of 14 letters in the sham group. Further vision loss may be attributed to the finding that in spite of continued treatment, progressive growth and persistent leakage of the neovascular lesion was seen angiographically – although less than in the control group. Doses of 1 mg and 3 mg showed no added benefits over the 0.3 mg dose. The effect was independent of lesion size or angiographic subtype, although subgroup analysis indicated a slightly larger benefit in minimally classic lesions, with stabilization in 76% of eyes compared to 54% in the sham group. At 54 weeks, patients in each pegabtanib group were rerandomized to continuous further pegabtanib treatment or sham treatment. Patients from the usual care group were distributed to continuous usual care, one of the three dose groups of pegabtanib or sham control. At 2 years, 59% of eyes receiving a dose of 0.3 mg lost < 15 letters versus 45% of usual care/sham-treated eyes (D’Amico et al. 2006) (Table 1). Six per cent of eyes in the pegabtanib group improved by three lines compared to 2% in the sham group (Table 2). Patients undergoing continuous retreatments maintained vision during the second year at the same level – a mean 2 line loss – as that documented after 12 months. Twenty-seven per cent of patients discontinuing pegabtanib treatment after the first year experienced an additional loss of ≥ 15 letters versus 16% in the continued treatment group, with the conclusion that injections of pegabtanib had to be continued throughout the entire 2 years to maintain the initial stabilization rates. Anatomically, the total lesion size in the group receiving the optimal drug dose of 0.3 mg continuously over 2 years increased over time from 3.7 DA at baseline to 5.5 DA at the 24 month follow-up. More than half of the patients were given additional PDT treatment at any time of follow-up. The group that received the highest number of PDT treatments – predominantly classic lesions – had a greater benefit in terms of both vision outcome and reduction in angiographic activity. At 2 years, there was an overall trend for predominantly classic lesions doing better with a continuous 0.3 mg dose treatment of pegabtanib, but in terms of statistical significance, no single subtype of CNV demonstrated any therapeutic superiority (Table 1). Severe vision loss was lowest in the predominantly classic lesion group: 6% at 24 months. At 2 years, a mean vision loss of 9–10 letters was found in all subgroups treated with pegabtanib at 0.3 mg with a mean of nine applied treatments per year (D’Amico et al. 2006).

Subsequent analysis revealed a moderately improved prognosis in a subgroup of patients with early lesions, i.e. vision > 54 letters and lesion size < 2 DA, with stabilization within 3 lines of loss in 76% with pegabtanib versus 50% in the usual care group (Gonzales 2005).

The ocular and systemic safety of the drug is excellent. Related to the intravitreal injection procedure, specific risks such as endophthalmitis (1.3% of treated cases during the first year, 0.7% during the second), traumatic lens injury (0.6% during the first year, 0.2% during the second) and retinal detachment (0.7% during the first year, 1.2% during the second) have to be considered. Preinjection antibiotics and povidone iodine treatment were identified as key elements of an efficient aseptic technique. Use of a lid speculum, sterile drap and sterile gloves are recommended.

**Recommendation**

Macugen has been approved by the FDA for all lesion types in neovascular AMD in the USA since December 2004 and by the European Medicines Agency (EMEA) for countries in the European Union since January 2006.

The recommended dose is 0.3 mg of pegabtanib. Patients treated throughout 2 years show a treatment benefit over patients receiving only 1 year of pegabtanib treatment. A mean of 16 out of 17 possible injections were administered to patients over 24 months. The therapeutic benefit is comparable to the one obtained with PDT monotherapy, with a lower number of treatments needed with PDT. However, a wider spectrum of lesions can be included and the prognosis appears to be independent of lesion size and composition. The chance of a significant improvement in VA is relatively low (6%).

**Recommendations are based on the VISION study data (evidence level I).**

**Intravitreal pharmacotherapy using ranibizumab (lucentis)**

**Rationale**

Ranibizumab is a recombinant, humanized Fab fragment of a monoclonal antibody with high affinity for VEGF. Because the binding site is located at aminoacid sites 88–89, ranibizumab binds and inactivates all isoforms of VEGF including the soluble VEGF fragments 110, 121 and 165 and the tissue-bound isoforms 189 and 206 (Chen et al. 1999). In animal models, intravitreal injection effectively reduced retinal and choroidal neovascularization as well as leakage from established vessels (Ferrara et al. 2003). Unlike the larger whole antibody, it has been shown to penetrate the retina easily and reach the subretinal space following intravitreal injection. Because of a short half-life time of 2–4 days of the short fragment and a rapid systemic clearance, the safety of ranibizumab is extremely high (Ferrara et al. 2003).

**Evidence**

In a first phase I/II study (FVF 2128), 53 patients were treated with repeated injections of 0.3 or 0.5 mg ranibizumab intravitreally. After 6 months, vision had improved by 3 lines in 45% of patients in the 0.5 mg...
group and was stable in 97.5% of treated eyes (Heier 2004).

Seven hundred and sixteen patients with minimally classic or purely occult CNV and evidence of presumed recent disease progression were included in the Minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of neovascular age-related macular degeneration (MARINA) trial, a randomized, multicentre, sham-controlled phase III trial. Patients received monthly injections of 0.3 or 0.5 mg of ranibizumab or sham treatment continuously over 24 months (Miller 2005).

At 12 month follow-up, 95% of ranibizumab-treated eyes compared to 62% of sham-treated eyes lost < 15 letters in VA (Rosenfeld et al. 2006). Visual improvement by ≥ 15 letters was found in 34% of eyes treated with a dose of 0.5 mg. At 24 months, 90% of eyes in the 0.5 mg group had continued to maintain stable vision without loss of > 15 letters compared to 53% in the control group (Rosenfeld et al. 2006) (Table 1).

A mean improvement of 7 letters was documented at 24 month follow-up. The prognosis in terms of vision maintenance as well as gain was independent of initial VA, lesion size or lesion composition. Thirty-three per cent of eyes in the 0.5 mg dose group improved by ≥ 15 letters; 42% of these patients ended up with a VA of 20/40 or better (Table 2). In both dose groups, ranibizumab prevented CNV growth and decreased the mean area of leakage angiographically. Typically, the functional and anatomical effect was seen rapidly within the first 3 months of intervention and was maintained throughout the entire follow-up of 24 months (Rosenfeld et al. 2006). Intraocular inflammation or presumed endophthalmitis was seen in 1.3% of eyes at 0.5 mg; lens damage and a retinal tear were documented in 0.4%. The 2 year cumulative number of deaths was 2.5% in the sham group and the 0.5 mg group and 2.1% in the 0.3 mg group. No significantly increased rate of systemic adverse events was found despite 2 years of continuous ranibizumab injections in 4 week intervals. In addition, ranibizumab-treated patients reported significant improvements in quality-of-life testing (NEI-VFQ-25) for near vision, distance vision and vision-specific dependency (Chang et al. 2006).

The Anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularization in age-related macular degeneration (ANCHOR) study comprised 423 patients with predominantly classic subfoveal CNV because of AMD in a prospective, randomized phase III trial design (Brown et al. 2006). Monthly injections of ranibizumab at 0.3 or 0.5 mg were compared to standard PDT, which was indicated at 3 month intervals, if leakage was seen angiographically. Ninety per cent of all eyes treated with ranibizumab at 0.5 mg lost less than 15 letters compared to 66% of eyes maintaining vision with PDT treatment alone at 24 months. Forty-one per cent of eyes in the higher dose group improved by ≥ 15 letters and 12% improved by ≥ 30 letters, compared to 6% of PDT-treated eyes (Table 2). In addition, these ranibizumab-treated patients demonstrated a mean improvement of 11 letters at 24 months and 38% had a final outcome of 20/40 or better. Initial VA or lesion size had no impact on vision prognosis. The rate of presumed endophthalmitis or uveitis was 0.7%. Death occurred at the same low rate (1.4–2.2%) in each of the different ranibizumab/PDT arms. In the 0.5 mg dose group, 4.3% of subjects experienced systemic arteriothromboembolic events. The frequency of myocardial infarctions was slightly higher in patients treated with 0.5 mg of ranibizumab than in the other two arms, although this difference was not statistically significant (Brown et al. 2006).

The PIER study, a phase IIIb trial, included 182 patients with all lesion types and evaluated the efficacy and safety of ranibizumab administered monthly for three doses followed by dosing every 3 months. While patients in the sham group lost a mean of 16 letters during 12 months of follow-up, patients with either dose of ranibizumab remained stable at baseline VA. Ninety per cent in the 0.5 dose group lost < 15 letters compared to 49% in the sham group; 13% versus 10% gained ≥ 15 letters (Schmidt-Erfurth & PIER Study Group 2006). The fact that the control group performed considerably worse than in the previous trials suggests that this was a different patient population. However, while the mean change in vision after three initial monthly ranibizumab injections was only slightly lower than the VA benefit achieved by the MARINA and ANCHOR trials, the overall VA in PIER returned to baseline from month 3 to month 12 after switching to quarterly dosing. This reduction in treatment benefit appears to highlight the need for a flexible regimen to maintain optimal results. A subgroup analysis revealed that 40% of PIER study patients were permanent gainers and maintained their initial benefit during long-term follow-up despite a reduction from monthly to quarterly reintimations. However, for the remaining 60% a reduced retreatment regimen was not appropriate and recurrent leakage activity and further vision loss occurred. Angiographic and optical coherence tomography (OCT) analysis revealed that a large proportion of patients experienced recurrent leakage and increased retinal thickness followed by VA loss (Mieler & PIER Study Group 2006). Obviously, an individualized retreatment regimen is required whereby retreatment is performed when recurrence is documented.

Safety was excellent: there were no incidences of endophthalmitis, traumatic lens or retinal injury and no arteriothrombolic systemic events in the PIER trial (Schmidt-Erfurth & PIER Study Group 2006).

In a phase IIIb, single-masked, multicenter, randomized study to evaluate the safety and tolerability of ranibizumab in naïve and previously treated subjects with CNV secondary to age-related macular degeneration (AMD) (SAILOR) trial, arteriothrombolic events occurred more frequently with the higher dose of 0.5 mg of ranibizumab compared to the lower dose of 0.3 mg with a treatment frequency of four treatments during 9 months and retreatments performed at the investigator’s discretion.

Recommendation

Lucentis has been approved by the FDA for all lesion types in neovascular AMD in the USA since July 2006. An approval by the EMEA for countries in the European Union was granted in January 2007.

The approved dose is 0.5 mg of ranibizumab.
The treatment regimen found to obtain optimal results in vision outcome was injections given monthly. A fixed regimen of quarterly injections was inferior to the monthly schedule. The overall rate of vision improvement was substantially lower under the quarterly PIER regimen compared to the monthly MARINA and ANCHOR regimen. Subgroup analysis indicated a proportion of patients with an initial and maintained vision gain compared to a proportion of patients losing the initial visual benefit with the fixed quarterly regimen. Therefore, an individualized retreatment indication is recommended, with a continuous diagnostic follow-up allowing treatment on demand when leakage activity and/or lesion growth recurs. The optimal treatment regimen offers patient management that is practical in terms of follow-up and retreatment rates and offers maximal systemic and ocular safety; affordable costs have yet to be determined. Appropriate studies (a randomized, double-masked, active-controlled, multicenter study comparing the efficacy and safety of ranibizumab (0.3 mg and 0.5 mg) administered as two dosing regimens in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration (EXCITE) trial, and a phase IIIb, open-label, multi-center 12 month study to evaluate the safety, tolerability and efficacy of ranibizumab (0.3 mg) in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration (SUSTAIN) trial) are underway. Diagnostic tools such as optical coherence tomography may offer useful parameters for retreatment decisions. Maintenance of vision can be expected in 90-95% and improvement by at least 3 lines was found in 30-40% of treated patients. All angiographic lesion types appear to respond favourably to the treatment. Frequent injections of ranibizumab are tolerated well for as long as 2 years. Ocular and systemic safety is extremely high. Risks and precautions to be taken in relation to the treatment procedure are identical to the experience with other antiangiogenic agents such as pegabtanib.

Recommendations are based on the ANCHOR, MARINA and PIER study data (evidence level I).

Combination therapy of antiangiogenic and photodynamic therapy

Rationale
Antiangiogenic therapy inhibits CNV-induced leakage and reduces progressive lesion growth, but appears to have little impact on CNV persistence which may require a permanent antiangiogenic intervention. Photodynamic therapy, on the other hand, is a safe and effective modality to directly target the neovascular membrane and induce an immediate thrombosis followed by atrophy. Combination of verteporfin therapy with an anti-VEGF adjunct may reduce the frequency of retreatments necessary and allow a permanent maintenance of the visual benefit specifically offered by antiangiogenic therapy.

Evidence
Combination with PDT and pegabta-nib was performed in a phase I/II study with improvement in vision by 3 lines in 60% of treated patients (Gragoudas 2005). More than half of the patients with predominantly classic lesions in the VISION trial received additional PDT treatments together with intravitreal pegabtanib injections and showed a beneficial course compared to the other lesion subtypes receiving PDT in only a minority of cases (Gragoudas et al. 2004). A phase I/II, single-masked multicenter study of the safety, tolerability, and efficacy of multiple-dose intravitreal injections of rhuFab V2 in combination with verteporfin (VISUDYNE) photodynamic therapy in subjects with neovascular age-related macular degeneration (FOCUS) trial, compared the safety and efficacy of ranibizumab in combination with PDT versus PDT alone in predominantly classic CNV. Previous PDT was allowed, and 52% of eyes had undergone unsuccessful prior PDT treatments (Heier et al. 2006). Patients received standard PDT followed by 0.5 mg of intravitreal ranibizumab 1 week after PDT or sham treatment. At 12 months, 91% of eyes in the combination group had lost < 15 letters versus 68% in the PDT monotherapy group. Twenty-four per cent of patients treated with combination improved by ≥ 15 letters compared to only 5% of patients undergoing PDT monotherapy. The proportion of 3 line gainers was highest (31%) if patients had not received any PDT previously and lowest (15%) when prior PDT had been used. A significant difference was found in the rate of PDT retreatments necessary: 3.4 treatments in the monotherapy arm compared to only 2.3 total PDT treatments in the combination arm. The hypolitized formulation of ranibizumab used exclusively in the FOCUS trial led to an increased rate of transient uveitis events, but the systemic safety was excellent (Heier et al. 2006).

In the open-label, multicenter, phase II study assessing the safety of Lucentis (ranibizumab) administered in conjunction with photodynamic therapy with Visudyne® in patients with occult or predominantly classic subfoveal choroidal neovascularization secondary to age-related macular degeneration (PROTECT) trial, patients with predominantly classic or occult lesions < 4 DA received same-day administration of standard PDT and intravitreal injection of the liquid formulation of ranibizumab used in the MARINA, ANCHOR and PIER studies, followed by three subsequent monthly injections of ranibizumab. Ninety-two per cent of eyes lost < 15 letters at 4 months. The mean improvement in vision was 7 letters; 25% of patients improved by > 15 letters (Schmidt-Erfurth et al. 2006). Ninety per cent of patients demonstrated a complete absence of leakage from CNV angiographically. Safety was excellent and an inflammatory response was not found in any case.

Recommendation
Combination of PDT and antiangiogenic agents such as macugen or Lucentis was safe and effective in predominantly classic lesions. The experience with other lesion types is limited. The prognosis in terms of vision maintenance and improvement appears to be similar to monotherapy with antiangiogenic substances; the eventually reduced need for retreatments might offer an alternative that is less time- and cost-intensive. Prospective clinical trials using a combination of verteporfin therapy and intravitreal ranibizumab administration (the 24-month randomized, double masked, controlled multicenter phase IIIb study assessing the safety and efficacy of verteporfin (Visudyne) photodynamic therapy administered in conjunction with
Lucantis versus Lucentis monotherapy in patients with subfoveal choroidal neovascularization secondary to age related macular degeneration (DENALI) and a 12-month randomized, double masked, controlled multicenter phase II study assessing the safety and efficacy of verteporfin (Visudyne) photodynamic therapy administered in conjunction with Lucentis versus Lucentis monotherapy in patients with subfoveal choroidal neovascularization secondary to age related macular degeneration (MONTBLANC) studies are currently evaluating this hypothesis.

Recommendations are based on the FOCUS and PROTECT study data (evidence level I and II).

Off-label therapy using bevacizumab (avastin)

Rationale

Bevacizumab is a full-length recombinant monoclonal antibody that is chemically related to ranibizumab. Accordingly, bevacizumab binds all VEGF isoforms and exerts its neutralizing effect by inhibiting the VEGF–receptor interaction, thus blocking vascular permeability and angiogenesis. The drug was developed to treat pathological angiogenesis in tumours and is approved by the FDA for the treatment of metastatic colorectal cancer, providing data on the safety of bevacizumab with repeated applications (Mculchy & Benson 2005). Because of its similar binding pattern for VEGF, it is hypothesized that bevacizumab may be as effective as ranibizumab in the treatment of neovascular AMD and other types of intraocular neovascularization. However, the larger molecular weight of bevacizumab (150 UD) and its lower binding affinity for VEGF may reduce its efficacy.

Evidence

In a phase I Systemic Avastin for Neovascular AMD (SANA) study on 15 patients, systemic bevacizumab therapy (two or three infusions of 5 mg/kg at 2 week intervals) provided significant improvement in VA, OCT and angiographic outcomes from baseline to 1 and 12 weeks (Michels et al. 2005). The only adverse event identified was a mild elevation in systolic blood pressure, which was controlled by antihypertensive medication.

A retrospective study included 81 eyes with subfoveal neovascular AMD that received intravitreal administrations of 1.25 mg of bevacizumab in monthly intervals until retinal edema, subretinal fluid and RPE detachment had resolved. No incidence of intraocular inflammation or toxicity was observed, nor were any systemic adverse events noted. Despite unsuccessful prior treatment with PDT and/or pegaptanib in 78% of eyes, a rapid reduction in retinal thickness, which is often associated with visual improvement, was observed. At 4 and 8 weeks, mean VA improved from 20/200 to 20/125 (Avery et al. 2006). Another retrospective study on 266 consecutive patients with CNV secondary to AMD treated with 1.25 mg of intravitreal bevacizumab during a 3 month period demonstrated similar results: at the 3 month follow-up, the mean VA had improved from 20/184 at baseline to 20/109 and 38% of patients experienced visual improvement (Spaide et al. 2006).

An electrophysiological study looked at changes in nine patients treated with 1.25 mg intravitreal injections. An improvement in multifocal electroretinography (m-ERG) macular function responses and relatively stable ganz-field electroretinography (G-ERG) responses were found, suggesting no obvious photoreceptor toxicity in the short term (Shahar et al. 2006). A similar study showed that injections of 2.5 mg were not toxic to the retina in a rabbit model; however, signs of toxicity were noted at 5 mg (Manzano et al. 2006).

Recommendation

Based on multiple uncontrolled and retrospective case series including large numbers of patients who were treated across the world with this off-label approach, bevacizumab appears to have a beneficial effect in the short-term treatment of intraocular neovascularization. However, because prospective randomized trials are missing, no solid proof of the level of efficacy has been provided. There are no long-term results on the safety and efficacy of the compound.

Each treatment decision is – legally and medically – based on an individual agreement between treating physician and patient and must be the consequence of a complete and comprehensive discussion of treatment alternatives, uncalculated risks and missing long-term experience. Informed consent regarding the benefits and risks and the off-label status of the drug is mandatory.

Recommendations are based on descriptive studies, case reports and expert opinion (evidence level III).

References


Chang TS, Fine JT & Bressler N (2006): Self-reported vision-specific quality of life at 1


