What is new in the management of wet age-related macular degeneration?

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Introduction or background: The hallmark of wet age-related macular degeneration (AMD) is choroidal neovascularization (CNV). The key cytokine involved in the pathogenesis of CNV is vascular endothelial growth factor (VEGF). Since 2005, antiVEGF therapy has revolutionized the management of this condition.

Sources of data: A systematic computerized literature search was conducted on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/).

Areas of agreement: AntiVEGF therapy has resulted in improvement in visual function and performance. Currently, practitioners are spoilt for choice of these agents.

Areas of controversy: Bevacizumab is unlicensed for intraocular use but has a better market share than ranibizumab in the treatment of wet AMD as it is approximately 40 times cheaper than ranibizumab, if aliquoted into smaller doses for intraocular use. This has stirred up questions on indemnity, safety, dosing, treatment regimen and quality control, despite the fact that well-designed clinical trials have shown that both drugs are equally effective. Another dilemma for the physicians is the choice of treatment regimens with antiVEGF agents that include fixed dosing, optical coherence tomography (OCT)-guided re-treatment, treat and extend or a combination of proactive and reactive dosing. Real-life outcomes of physician-dependent OCT-guided re-treatment with these agents are inferior to outcomes reported in clinical trials.

Growing points: A recently food and drug administration-approved antiVEGF agent, aflibercept, is rapidly becoming a popular choice as well-designed randomized clinical trials indicate that eight weekly fixed dosing of aflibercept is non-inferior to monthly ranibizumab.

Areas timely for developing research: Options for reducing the frequency of repeated intravitreal injections are being explored. Combination therapy with photodynamic therapy and epimacular brachytherapy seem scientifically plausible due to their synergistic effects. However, so far the results on these combinations have not shown any superior visual outcomes to antiVEGF monotherapy, and the practicalities of delivering these therapies are formidable. So, research into other novel therapeutic approaches such as pigment...
epithelium-derived factor and designed ankyrin repeat proteins are gaining momentum.

Keywords: age-related macular degeneration/VEGF/ranibizumab/aflibercept/bevacizumab/radiation

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Introduction

Age-related macular degeneration (AMD) is the leading cause of visual impairment in individuals over the age of 55 years in the developed world.\(^1\) Wet or neovascular AMD affects only 10–15\% of AMD patients, but accounts for approximately 90\% of blindness due to this condition.\(^2\) The main cause of vision loss in wet AMD is the development of choroidal neovascularization (CNV) characterized by the abnormal growth of new blood vessels from the choroid into or underneath the retina. Vascular endothelial growth factor-A (VEGF-A) is the key cytokine closely associated with the growth and permeability of these new blood vessels.\(^3\)

The treatment of neovascular AMD has evolved considerably over the past 40 years. Whereas the results of previous treatment modalities such as thermal laser photocoagulation\(^4\) and photodynamic therapy (PDT) with intravenous verteporfin\(^5\) were disappointing, the introduction of drugs that directly inhibit the actions of VEGF has provided patients with hope for improvement of vision.\(^6\) Three antiVEGF drugs have been used for over 5 years, i.e. pegaptanib (Macugen\(^\circledast\); Eyetech Inc., FL/Pfizer Inc., NY, USA introduced in 2004), bevacizumab (Avastin\(^\circledast\); Genentech, South San Francisco, CA, USA/Roche, Basel, Switzerland, first used off-label in 2005) and ranibizumab (Lucentis\(^\circledast\); Genentech, South San Francisco, CA, USA/Roche, Basel, Switzerland, introduced in 2006), whereas aflibercept (VEGF Trap-eye, Eylea\(^\circledast\); Regeneron, Tarrytown, NY, USA/Bayer Plc, UK) has just been granted regulatory approval in the UK in 2012.\(^7\) Pivotal trials with ranibizumab, bevacizumab and aflibercept show that patients receiving protocol-driven treatment have a 30–40\% chance of achieving a 15-letter improvement in visual acuity.\(^8\)–\(^11\) The rapid adoption of these drugs by physicians has resulted in dramatic increase in public awareness and patient expectations. Modelling of visual acuity outcomes from phase 3 ranibizumab trials to incidence rates of neovascular AMD from population-based studies shows that monthly ranibizumab for 2 years should have a substantial effect on reducing the magnitude of legal blindness and visual impairment within 2 years after diagnosis.
of neovascular AMD among non-Hispanic white individuals in the USA.\textsuperscript{12} Real-life data from Germany and UK also show comparable figures.\textsuperscript{13,14}

**Initiation of antiVEGF therapy**

If left untreated, subfoveal CNV may grow quickly, on average around 10 $\mu$m per day.\textsuperscript{15} So, prompt treatment with antiVEGF therapy is recommended. Ideally, treatment within 2 weeks of diagnosis is recommended. The risk of increasing visual loss is higher if treatment is delayed by more than a month.\textsuperscript{15} The loss of vision while awaiting re-treatment from point of decision to re-treat is also significantly greater than the gain of vision after re-initiation of therapy.\textsuperscript{16}

**Choice of drug**

Since 2005, patients and their ophthalmologists have faced a dilemma of choosing between the two closely related drugs (ranibizumab and bevacizumab) in treating neovascular AMD. Bevacizumab is not a generic form of ranibizumab; ranibizumab and bevacizumab are different molecules produced in different cell culture systems. Although both are murine-derived humanized monoclonal antibodies, the active binding site of ranibizumab has been affinity matured to produce stronger binding. Bevacizumab (149 kDa) is larger than ranibizumab (48 kDa), but retinal penetration studies have not shown conclusive evidence of poorer penetration by bevacizumab. Bevacizumab also includes the Fc portion so it may be a more potent antigenic stimulus.\textsuperscript{17} Ranibizumab has been rigorously tested for use in neovascular AMD patients, whereas bevacizumab has been rigorously tested for intravenous use in colorectal cancer patients. However, the presumed equivalent efficacy and the fact that ranibizumab is 40 times as costly as bevacizumab engineered several head-to-head trials around the world.

The comparison of AMD treatment trials (CATT) study examined the efficacy, dosing and cost-effectiveness of ranibizumab and bevacizumab for the treatment of neovascular AMD.\textsuperscript{10} This prospective, randomized, trial revealed a significant improvement in vision with both treatments in terms of visual acuity. Monthly treatment with the drugs resulted in similar increases in visual acuity. However, at year 2, treatment as needed resulted in less gain in visual acuity, whether instituted at enrolment or after 1 year of monthly treatment. Ranibizumab was superior in terms of reducing retinal fluid and leakage over a 2-year period. The interim analyses of the health technology assessment
## Table 1  Comparative studies of different antiVEGF agents in wet AMD.

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Treatment arms</th>
<th>Re-treatment</th>
<th>Key efficacy data</th>
</tr>
</thead>
</table>
| **CATT**¹⁰  | To evaluate the relative efficacy and safety of treatment of wet AMD with bevacizumab when compared with ranibizumab | Total n = 1208  
In year one  
Ranibizumab 0.5 mg monthly n = 301  
Bevacizumab 1.25 mg monthly n = 286  
Ranibizumab 0.5 mg 1 + PRN n = 298  
Bevacizumab 1.25 mg 1 + PRN n = 300  
In year 2  
Those initially randomized to monthly re-randomized to 50% continuing on monthly treatment and 50% to PRN | If signs of active CNV  
- Eyes with fluid on OCT should be treated, unless there has been no decrease in fluid after three injections  
- If no fluid on OCT, but any signs of active CNV, treat.  
- Patients who present for a 'non-scheduled' visit may be treated if they meet re-treatment criteria at least 4 weeks since last injection. | Primary endpoint: Mean change in visual acuity after 1 year with a non-inferiority limit of five letters (ETDRS)  
Year 1/year 2 data  
Ranibizumab 0.5 mg monthly = +8.5/+8.8  
Bevacizumab 1.25 mg monthly = +8.0/+7.8  
Ranibizumab 0.5 mg PRN = +6.8/+6.7  
Bevacizumab 1.25 mg PRN = +5.9/+5.0  
Number of injections year 1/year 2  
Ranibizumab monthly 11.7/22.4  
Bevacizumab monthly 11.9/23.4  
Ranibizumab PRN 6.9/12.6  
Bevacizumab PRN 7.7/14.1. |
| **IVAN**¹⁸  | To evaluate the relative efficacy and safety of treatment of wet AMD with bevacizumab when compared with ranibizumab  | Total n = 600  
In year 1  
Ranibizumab 0.5 mg monthly n = 150  
Bevacizumab 1.25 mg monthly n = 150  
Ranibizumab 0.5 mg 3 + PRN x 3 (n = 150)  
Bevacizumab 1.25 mg 3 + PRN x 3 (n = 150)  
2-year results and the primary expected in early 2013 | Retreatment criteria  
Monthly visits, if active disease on OCT, or VA, ↓ in past 3 months, get three consecutive monthly injections. | Interim analyses at year 1—bevacizumab vs. ranibizumab was inconclusive (bev–rani = −1.99 letters)  
Discontinuous—continuous = −0.35 letters |
Studies designed to demonstrate non-inferiority of a range of aflibercept dosing schedules to monthly intravitreal injection of ranibizumab 0.5 mg

VIEW 1 & 2

Multicentre, active controlled, double-masked non-inferiority—identical trials VIEW 1 n = 1217; VIEW 2 n = 1240

Year 1
Treatment is fixed and protocol mandated. All patients are seen every 4 weeks for VA checks and safety review—those in the eight weekly treatment arms receive a sham injection at this visit. Note: visits and, thus, treatment are based on four or eight weekly basis and not calendar months.

FA
New macular haemorrhage
Regardless of these criteria, all patients must be treated at a minimum of every 12 weeks.

Year 2
Treatment is described as ‘Capped PRN’. All patients reviewed every 4 weeks and can be treated if they meet re-treatment criteria.
- Increase in CRT > 100 µm when compared with lowest previous value
- VA loss ≥ 5 letter + fluid on OCT
- New or persistent fluid on OCT
- New onset classic choroidal neovascularisation
- New or persistent leak on FA
- New macular haemorrhage
Regardless of these criteria, all patients must be treated at a minimum of every 12 weeks.

Primary endpoint was at 52 weeks and was the percentage of eyes losing <15 letters.

Percentage of eyes losing <15 letters VIEW 1/View 2
Ranibizumab 0.5 mg four weekly 94.4/94.4
Aflibercept 0.5 mg four weekly 95.9/95.6
Aflibercept 2 mg four weekly 95.1/95.6
Aflibercept 2 mg eight weekly 95.1/95.6

Change in BCVA from baseline Year 1/2
Ranibizumab 0.5 mg four weekly 8.7/7.9
Aflibercept 0.5 mg four weekly 8.3/6.6
Aflibercept 2 mg four weekly 9.3/7.6
Aflibercept 2 mg eight weekly 8.4/7.6

Number of injections year 1/2
Ranibizumab 0.5 mg four weekly 12.3/4.7
Aflibercept 0.5 mg four weekly 12.2/4.6
Aflibercept 2 mg four weekly 12.3/4.1
Aflibercept 2 mg eight weekly 7.5/4.2.

FA, fluorescein angiography; VA, visual acuity.
The benefits of both bevacizumab and ranibizumab are maximal when used as a fixed, monthly dosing regimen. However, the impact of monthly dosing regimens on the burden on patients and health care is enormous (Table 1). So in real life, practitioners elect to use variable re-treatment regimens. The goal of such regimens is to maintain the same visual benefit as monthly dosing while easing the cost and time burden on patients and families. The PrONT0 study suggested that a pro re nata (PRN) approach to re-treatment could meet the goal of visual maintenance while easing the treatment burden. However, several reports from real life have failed to replicate the results of the PrONT0 study. This led to the two large multicentre clinical trials (CATT study in the USA and IVAN study in the UK) to compare fixed monthly dosing with discontinuous dosing as one of their research objectives. The CATT study showed that the PRN dosing and continuous dosing were equivalent in the ranibizumab arms, but the equivalence of the PRN dosing of bevacizumab to the monthly treatment was inconclusive. The PRN regimen was generally associated with a larger lesion size after 12 months when compared with the fixed treatment regimens. Treatment as needed resulted in less gain in visual acuity, whether instituted at enrolment or after 1 year of monthly treatment.

The CATT study also evaluated the impact of switching to as-needed treatment after 1 year of monthly treatment. Switching from monthly to as-needed treatment resulted in greater mean decrease in vision during year 2. So, CATT study demonstrated that treatment as needed resulted in less gain in vision whether instituted at enrolment or after 1 year of monthly treatment.

Almost all studies showed that PRN dosing does not have the same levels of efficacy as the monthly injections studied in MARINA and ANCHOR. The goal of maintaining visual acuity after the initiation phase by pre-empting active disease without monthly injections is yet to be achieved. Recently, a combination of reactive and proactive dosing has been recommended in the second year of the VIEW studies and the FUSION regimen. In this dosing regimen, a mandatory injection is given at fixed intervals, despite the absence of disease activity (proactive) while the reactive dosing is performed when monthly
monitoring by optical coherence tomography (OCT) and/or visual acuity shows disease activity.

Undertreatment was observed in approximately 28% of the re-treatment visits in the CATT study. This suggests that physician-dependent re-treatment criteria are not an ideal option for optimal vision gain. So, the availability of this new drug, aflibercept (VEGF Trap-eye; Regeneron Pharmaceuticals, Tarrytown, NY, USA; Bayer Plc) has gained considerable interest among patients and physicians. Aflibercept is a recombinant human fusion protein that acts as a soluble decoy receptor for VEGF family members VEGF-A, VEGF-B and placental growth factor, thereby preventing these ligands from binding to, and activating, their cognate receptors. The efficacy of intravitreal aflibercept in the treatment of neovascular AMD has been compared with that of intravitreal ranibizumab, the current gold standard for this indication, in two pivotal phase III studies of virtually identical design (VIEW 1 and 2). In both trials, the recommended regimen of aflibercept [2 mg every second month (after three initial monthly doses)] was shown to be non-inferior to the recommended regimen of ranibizumab (0.5 mg every month) in terms of the primary endpoint of the proportion of patients who maintained their vision after 1 year of treatment; similar results were seen when monthly dosing with aflibercept (0.5 or 2 mg) was compared with ranibizumab. Over a period of 96 weeks in the VIEW studies, patients receiving the recommended regimen of aflibercept during the first year, followed by modified quarterly treatment during the second year had a similar visual acuity gain to those receiving the recommended regimen of ranibizumab during first year, followed by modified quarterly treatment during the second year, but on average required five fewer injections. Aflibercept was generally well tolerated in the VIEW studies; the ocular and non-ocular adverse event profile of the drug was similar to that of ranibizumab. So, physicians and patients are looking forward to use this drug with the aim of reducing hospital appointments without compromising visual outcome.

Safety concerns

The risk of aliquoting bevacizumab by different pharmacies was not assessed in the CATT study as the drugs were supplied in glass vials and wiped with alcohol prior to withdrawing medication according to a specific protocol. There were no differences between drugs in rates of death or arterio-thrombotic events. The interpretation of the persistence of higher rates of serious adverse events with bevacizumab attributable to hospitalizations for infections and to gastrointestinal...
disorders such as hemorrhage, nausea and vomiting remains uncertain. Other than bleeding, there was a lack of specificity of these serious adverse events to conditions associated with inhibition of VEGF. However, a recent report based on safety events in five trials on ranibizumab has alerted an increased risk of cerebrovascular accidents (CVA) with ranibizumab. Pooled 2-year CVA rates were <3%; odds ratios (95% confidence intervals) for CVA risk were 2.2 (0.8–7.1) for 0.5 mg ranibizumab versus control. The difference between 0.5-mg ranibizumab and control was larger [7.7 (1.2–177)] among high-risk CVA patients.

**Combination treatments**

Another option to reduce this burden of care is to reduce the number of injections required by combining the anti-VEGF therapy with another treatment. PDT with verteporfin has a demonstrated benefit for predominantly classic wet AMD and has been tried in combination with anti-VEGF therapy to evaluate its additive effect. Although combination therapy appears to be scientifically plausible, safe and effective, comparative studies on combination therapy have not shown any superior visual acuity outcomes when compared with anti-angiogenic monotherapy. Ranibizumab in combination with PDT has been studied in the FOCUS and PROTECT studies. Both studies showed that the combination group exhibited less lesion growth and greater reduction in CNV leakage and subretinal fluid accumulation. The MONT BLANC study showed and confirmed the non-inferiority of combination therapy over ranibizumab monotherapy at 12 months. So, combination therapy may be useful for those patients who may have difficulty with follow-up. Importantly, the study showed that the number of injections required in the combination arm did not differ significantly from that of the monotherapy arm. So, this treatment can be beneficial in selected cases only.

Considerable evidence suggests a potential benefit for using radiation therapy to treat neovascular AMD. Early external beam radiation therapy studies produced equivocal results and suggested that fractionated doses are less likely to cause radiation retinopathy. Newer modalities, such as proton therapy, stereotactic radiation therapy (SRT) and epimacular brachytherapy, allow enhanced precision and accuracy and, thus, permit larger doses per fraction. Proton therapy has the highest risk of radiation retinopathy. SRT with 24 Gy in a single fraction, as delivered by the IRay, generates less internal scatter; however, its widespread use may be limited by the need for the hospitals to purchase and gain expertise with the device. Epimacular radiotherapy...
offers very precise dosing of large fractions at the expense of requiring a vitrectomy that leads to cataract formation in up to 80% of patients with phakic eyes at baseline. However, the vitrectomy itself may be beneficial in treating AMD.\textsuperscript{28} Although these therapies may reduce the need for intravitreal injections, the practicality of offering these options as first-line treatment for patients with neovascular AMD is remote. They may be helpful in selected patients, although the phenotype that benefits from this combination remains unclear.

**Conclusion**

A clinician initiating a patient with neovascular AMD on antiVEGF treatment must make an informed decision on their choice of antiVEGF agent. Bevacizumab is not formulated for intravitreal use, but aliquoted doses of this drug are widely used ‘off-label’ to treat AMD. In such cases, patients should be fully informed regarding their treatment and any potential risks involved. Off-label use of a drug may be an option in countries with unmet medical need. However, the use of an unlicensed or ‘off-label’ medicinal product, when a suitable licensed alternative is available, puts prescribing physicians at risk of liability, if safety issues arise.\textsuperscript{29} Economic considerations is the most likely influencing factor in the selection of drug for individual patients.\textsuperscript{30} Physicians may also be slightly less comfortable choosing between physician-guided variable dosing over fixed dosing, if the tendency for undertreatment among physicians opting for variable dosing is high. If aflibercept allows for an eight weekly dosing of the drug and is cost-effective, it is likely that there may be a paradigm shift to eight weekly fixed dosing of aflibercept in future.

**Conflict of interest**

S.S. and P.H. have received research grants, travel grants, speaker fees and have attended advisory board meetings of Novartis, Bayer, Pfizer and Allergan.

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