Molecular therapies for AMD

Victor Chong describes some of the latest developments in AMD treatment and describes the role of angiogenic factors and how they may be manipulated (C4243, one standard CET point)

OPHTHALMOLOGY IS A FAST moving field. In the past 25 years,for example, we have seen amazing strides in the field of cataract surgery. Many of us still remember aphakic glasses.

When 'one-stitch' cataract surgery was first introduced, we were impressed but assumed it was going to be for the select few.

Sutureless, spectacle-independent cataract surgery, performed under topical anaesthesia, is now the norm.

The progress of therapeutic developments for retinal diseases, in particular age-related macular degeneration (AMD), was slow in the 20th century. The 21st century is quite a different story. If we can continue the pace of progress seen in the last five years over the next 20 years, I will be confident of facing AMD myself in my senior years.

In this review, I aim to outline the concept of molecular therapy. With particular reference to AMD, the article will describe angiogenesis, vascular endothelial growth factor (VEGF), and choroidal neovascularisation (CNV).

CLASSIFICATION AND PREVALENCE OF AMD

The classification and nomenclature of AMD has changed from time to time and led to some confusion in the ophthalmic community.

In this article, I will use the term 'early dry AMD' (as opposed to age-related maculopathy, ARM) to include all those patients with drusen, pigmentary changes and localised focal atrophy. Geographic atrophy involving the fovea is 'late dry AMD', while choroidal neovascularisation and pigmented epithelial detachment are 'late wet AMD'. A few small drusen are considered as normal.

Based on the estimation from data pooled from three large population studies in the US, Europe and Australia, among the over-75s, about 6 per cent have early dry AMD, 2 per cent have late dry AMD and 4 per cent have late wet AMD. So AMD, on the whole, affects about 12 per cent of the population among this age group.

Furthermore, population surveys tend to under-estimate diseases due to selection bias towards healthier individuals.

Late AMD was the cause of sight loss in 53 per cent of blind registrations in the UK in 2002 and AMD is, therefore, a major public health issue.

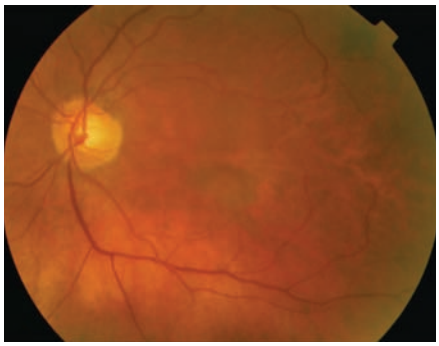

FIGURE 1. Predominantly classic CNV

Choroidal neovascularisation is subdivided into at least three clinical subtypes based on fluorescein angiogram. There are some suggestions that they might respond to treatments differently.

1 Predominantly classic CNV (Figures 1 and 2) – over 50 per cent of the lesion is a classic CNV
2 Minimally classic CNV – classic CNV is present but less than 50 per cent of the lesion
3 Pure occult CNV (figures 3 and 4) – no classic CNV is present.

CHOROIDAL NEOVASCULARISATION AND ANGIOGENESIS

Choroidal neovascularisation (CNV) describes choroidal vessels that have invaded the retina after breaking through Bruch's membrane. There were numerous hypotheses for the cause of CNV. It appears to be a balance of local oxygen tension changes, retinal pigment epithelial cell damage, inflammation, and the break down of the physical barrier of Bruch's membrane. The latter explains why CNV tends to occur in the fovea where the physical barrier is weakest, and why large laser burns damaging the Bruch's membrane can cause CNV in healthy animals.

The mechanism of the proliferation of choroidal vessels is similar to all forms of new vessel formation (angiogenesis). Angiogenesis is important during development of normal vasculature in foetal development and normal growth. Similarly, it is a normal physiological process in healing. However, it can work against the body for instance in tumour growth. All forms of malignant tumour can 'up regulate' the angiogenesis to increase blood supply to the new tumour tissues. In CNV, it is really a healing process 'gone wrong', with local destruction of the retina and hence vision loss.

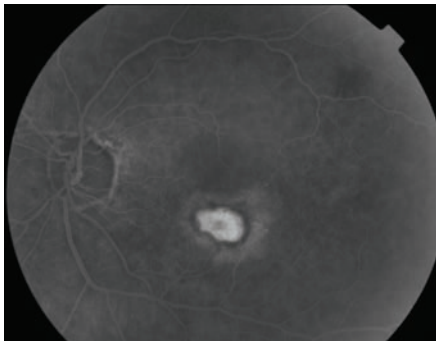

FIGURE 2. Angiogram of classic CNV

Angiogenesis involves a number of well controlled physiological pathways. No matter what the aetiology, when an area of the body requires more nutrients, ie blood supply, a signal is sent to the nearby vascular structures. These structures, in return, start a cascade of signal amplification, involving surrounding immune cells. One of the key elements of the initialisation/amplification process is a growth factor called vascular endothelial growth factor (VEGF).

It remains uncertain whether VEGF is involved in the initialisation phase or the amplification phase in AMD but, one way or another, it plays a key role. This may be deduced from observations of blocking VEGF in a number of angiogenesis experimental models, all resulting in significant reductions in angiogenesis.

Although we are not going to discuss

diabetic retinopathy in detail, it is important to remember that VEGF plays a critical role in the pathogenesis of proliferative diabetic retinopathy (retinal angiogenesis) and diabetic maculopathy (leakage).

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

Translating the uncertainty of laboratory science into clinical practice has always led to significant confusion. Vascular endothelial growth factors are a group of similarly structured growth factors which play a key role in vascular and lymphatic proliferation. So 'VEGF' is not a single factor. Furthermore, most of these growth factors have more than one function and different functions in different cell types.

In addition to supporting endothelial cell growth and multiplication, VEGF can increase vascular leakage, support tubular formation of small vessels and protect neuronal cells.

In CNV formation, VEGF-A is probably the most important factor and will be referred to as VEGF for the remainder of this article. Even within VEGF-A, there are different isoforms (different sizes of molecule) which play slightly different functions. The most important isoform within the eye is VEGF165, though VEGF121 and VEGF183 are commonly found too. To complicate the matter further, different terminal isoforms have recently been identified. They are named VEGFxxxb, where 'xxx' is the isoform number (for example, VEGF165b). These different isoforms might have the opposite biological effect to the 'original' isoforms. In other words, the VEGFxxxb might inhibit angiogenesis rather than promoting it.

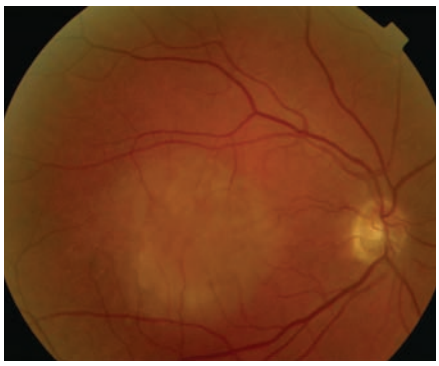

FIGURE 3. Ocular CNV

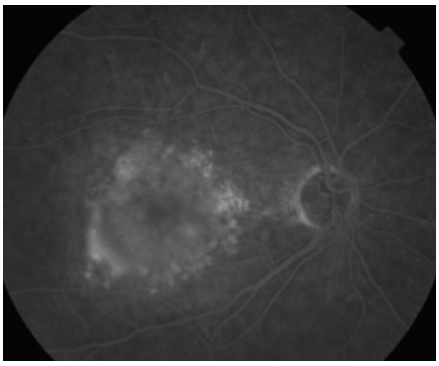

FIGURE 4. Angiogram of occult CNV

TABLE 1

Proportion of eyes with <3 lines of visual acuity loss with Predominantly classic CNV

Therapy	Trial	Treated	Control
Visudyne	TAP investigation	67%	40% (Placebo)
Macugen	VISION	68%	57.5% (Usual care)
Lucentis	ANCHOR	94%	64% (Visudyne)

MOLECULAR THERAPY – PRINCIPLE AND PRACTICE

The principle of drug treatment varies significantly in different diseases. For instance, in antibiotic treatment of infection, the antibiotic destroys the bacterial cell membrane. So the drug destroys the cause of the disease. In ▶

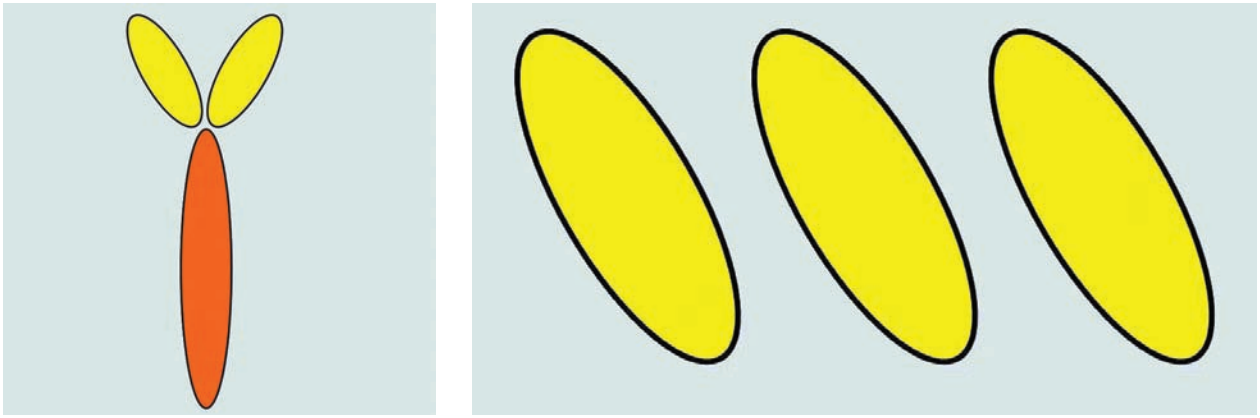

FIGURE 5. Diagrammatic representation of a full size anti-VEGF molecule Avastin (a) and fragment of anti-VEGF molecule Lucentis (b).

hypertensive treatment using calcium channel blockers, it is a totally different story. Calcium channel blockers, as the name suggests, block calcium channels and so cause vasodilatation, leading to reduction of blood pressure. So no matter what the cause of the high blood pressure, it would work. In the history of drug discovery, many were found by accident and many of these molecules were plant extracts. The mode of action was often discovered later.

Molecular therapy attempts to take a more logical approach. For instance, in anti-angiogenesis therapy, VEGF was first identified as one of the main players in angiogenesis. The conceptual idea was that blocking VEGF might reduce angiogenesis and hence provide a therapeutic solution to excessive angiogenesis, such as seen in cancer and CNV. The blockers are then specifically designed and related to the known molecular structure of VEGF.

There are many steps in the action of VEGF where an intervention may be made. VEGF has to be produced locally, then has to cleave to reach its receptors. Then the receptors induce a response cascade within cells leading to its action. The cascade may be blocked by kinase inhibitors. The production of either VEGF or its receptors may be inhibited by using interference RNA technology. A decoy soluble receptor (a 'VEGF trap') can be used to 'capture' the VEGF before it reaches its receptor. The latter two modes of therapy have recently been the subject of promising initial Phase I data. Similarly, aptamer and humanised monoclonal antibody can also block VEGF from reaching its receptors.

Macugen (Pegaptanib) – Aptamer of VEGF165

Aptamers are single-stranded nucleic acids that directly inhibit a protein's function by folding into a specific three-dimensional structure that affords high-affinity binding to the targeted protein. Macugen is highly specific and binds to VEGF165 only, without binding to other isoforms. The obvious benefit of the high degree of specificity is that normal vascular maintenance would not be disrupted. However, in AMD, normal vascular maintenance is probably not that important unless the patient is also treated with photodynamic therapy, during which temporary choroidal shutdown is a common feature.

Macugen was approved by the FDA (US) in December 2004 and has just received approval in the UK. According to the manufacturer of Macugen, over 200,000 injections were given in the first year of sale.

In the VISION study, a combination of two large-scale double-masked randomised controlled trials, Macugen was significantly better than usual care in all forms and different sizes of CNV. However, if the two studies were analysed separately, treatment of minimally classic CNV shows consistent results between the two studies, but inconsistency exists for treatment of predominately classic CNV and pure occult CNV. This can happen purely by chance, but may be due to the relative usage of photodynamic therapy or patient selection differences in the two study groups (they took place in different locations). There is, as yet no official head to head comparison of Macugen with PDT.

The results are summarised in Tables 1 and 2. Three lines' loss of vision is the equivalent of a doubling of the visual angle and is considered to be significant moderate visual loss. So it represents an acuity drop from 6/12 to 6/24, or 6/18 to 6/36, or 6/24 to 6/48.

Lucentis (Ranibizumab) – a monoclonal antibody fragment of VEGF

Any animal will generate an antibody against a foreign molecule, such as a bacterium or a molecule from another animal. The antibody is usually very specific (monoclonal) and manages to attach to the foreign molecule. The antibody can be diagrammatically shown as a 'Y' shaped structure (Figure 5a). The two 'arms' attach to the foreign molecule while the leg of the 'Y' is the receptor region which is recognised by the immune system. So the antibody helps to 'catch' the foreign molecule for the immune system. In order to produce an antibody to human VEGF, one has to use another animals as human VEGF would not be considered as foreign by the human body. So a biotech company developed a mouse monoclonal anti-human VEGF. The mouse antibody is humanised so that it does not induce a significant immune response when given to humans. In order to make the molecule smaller, so it can get through the whole retina, the 'Y' humanised mouse anti-VEGF is broken up, leaving the arms with the attachment part only (Figure 5b). The end product is Lucentis which is a fragment of humanised mouse monoclonal anti-VEGF. As it attaches to the VEGF region 85 to 87, it would bind to all known isoforms of VEGF, as the smallest isoform is VEGF110. It would, therefore, block both pro-angiogenic and anti-angiogenic isoforms of VEGF. The latter is clearly a potential problem.

TABLE 2

Proportion of eyes with <3 lines of visual acuity loss with Minimally classic or Occult CNV (The data on VISION and MARINA were estimated based on presented data)

Therapy	Trial	Treated	Control
Visudyne	VIP (Occult) VIM (MC)	49% 72%	45% (Placebo) 53% (Placebo)
Macugen	VISION (Occult) VISION (MC)	66% 76.5%	64.5% (Usual care) 54.5% (Usual care)
Lucentis	MARINA (Occult) MARINA (MC)	94% 96%	62% (Sham) 62% (Sham)

However, the clearance of the drug within the eye is rapid, so the total VEGF blockade is probably transient.

At the time of writing (April 2006), the data for Lucentis has not been peer-reviewed, so all presented data should be considered as preliminary. The MARINA study compared Lucentis with sham treatment in patients with minimally classic and pure occult CNV. The ANCHOR study compared Lucentis (with sham PDT) with PDT treatment (with sham injection) in patients with predominantly classic CNV, ie a head-to-head for Lucentis vs PDT. The results are summarised in Tables 1 and 2.

COMPARING MACUGEN TO LUCENTIS

There is no head-to-head between these two drugs, so the efficacy cannot be directly compared. Most retinal specialists believe that Lucentis is better than Macugen based on the following information:

◆ In all study groups, no matter the type of CNV, the size of the CNV and the initial vision acuity, a Lucentis treated group has, on average, significant improvement in vision and the controlled groups have, on average, reduction in vision. With Macugen treatment, the average vision was significantly better than for the sham treatment, but it was worse than baseline in the Macugen treated group

◆ The results are consistent within both Phase 3 study (MARINA and ANCHOR), though admittedly they have different entry criteria

◆ The sub-group analysis of the VISION study of patients with early disease did have better visual outcome but still not as good as that of Lucentis. One suggestion is that the study patients in VISION (Macugen study) had worse disease.

SO WHY USE MACUGEN OR VISUDYNE?

At the moment, Macugen is injected every six weeks and Lucentis is injected every four weeks. So over 12 months, it is nine injections as compared to 13 injections. There are several ongoing studies to see whether Lucentis can be injected less frequent but so far there is no data. Macugen has three years of clinical trial data and over 12 months of widespread clinical use as compared to Lucentis has only 12 months clinical data (although 24 months are due out in May 2006). The total blockage caused by Lucentis might be a potential problem, although, as mentioned before, the short half-life of Lucentis in the eye and the planned reduced injection frequency might reduce this risk.

Although the price is not confirmed, it is suggested that Macugen would be around £500 per injection as compared to £1,150 for Lucentis, so over 12 months in full protocol, the drug cost alone will be £4,500 for Macugen and £14,950. If we use Lucentis as the treatment for the first three injections and then follow with seven Macugen injections as maintenance, the drug cost would be £6,950. So if Macugen is good enough for maintenance, this would be more cost effective. Similarly, if we only need seven Lucentis injections per year with the same result as full 13 injections protocol, it would cost £8,050.

Combination of Visudyne photodynamic therapy with Lucentis or Macugen might give even better outcome or might reduce frequency of injections, so PDT use is likely to be continued. Although the intravitreal injections are well tolerate, not everyone can tolerate the injection, so Visudyne would remain the treatment of choice.

SO WHAT ABOUT OTHER RETINAL DISEASES?

Phase 3 clinical trials are now under way looking at both Macugen and Lucentis for diabetic maculopathy. As mentioned, VEGF is a key factor in vascular leakage, so it might be more useful. The only problem is the multiple injections for a chronic disease such as diabetes. Nonetheless, this is against the background of a relatively poor visual outcome with laser treatment in those with diffuse macular oedema. Phase I/II studies are also underway for macular oedema associated with retinal vein occlusion. This might be more promising as the condition is not as chronic as diabetes. Combination therapy with laser is also likely to reduce the number of injections.

THE FUTURE

In the short term, we will have to develop different treatment strategies using current or shortly available therapies in combination with different dosage, treatment frequency or treatment sequence. In the medium term, some form of maintenance therapy without injection should become available.

At the same time, a prevention of the conversion from dry to the wet form of AMD might become available. Surgical management of wet AMD, such as macular translocation, might improve further but after so many years of development, the results are still relatively poor. Randomised controlled trials comparing macular translocation with medical treatment, such as Lucentis, are urgently needed. Transplantation of RPE cells or stem cells with the removal of CNV might be more successful in the future but it is still very much in its infancy.

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MULTIPLE-CHOICE QUESTIONS

1 What percentage of the over-75s have 'late wet' AMD in the US, Europe and Australia?
A 6 per cent
B 2 per cent
C 4 per cent
D 12 per cent

2 Which of the following is not a function of VEGF?
A Supports endothelial growth and multiplication
B Decreases vascular leakage
C Supports tubular formation of small vessels
D Protects neuronal cells

3 Which of the following is likely to be the most important isoform within the eye?
A VEGF-A
B VEGF121
C VEGF183
D VEGF165

4 What is an aptamer?
A An isoform of VEGF
B The part of an antibody attached to a pathogen
C A decoy soluble receptor
D A single strand nucleic acid affording high affinity binding to the targeted protein

5 What is the accepted delivery of treatment with Macugen?
A 6 weekly injection
B 4 weekly injection
C Weekly oral administration
D One-off injection with 'cold' laser intervention

6 Which of the following common eye diseases is unlikely to benefit from the latest developments in anti-angiogenesis?
A Primary open angle glaucoma
B Ischaemic central retinal vein occlusion
C Diabetic maculopathy
D Proliferative retinopathy

The deadline for responses is July 20

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