Southampton
University Hospitals NHS Trust

Ophthalmology Directorate
Ophthalmology
Southampton Eye Unit,
Mail point 104
Southampton General Hospital
Tremona Road
Southampton SO16 6YD

[redacted]

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Personal Statement by Professor Andrew Lotery for NICE appraisal of pegaptanib and ranibizumab for the treatment of age-related macular degeneration

What is the place of the technology in current practice?

AMD (age-related macular degeneration) is the commonest cause of legal blindness in the western world. The most severe form of AMD is called "wet AMD". This is a condition where new blood vessels arising from the choroid grow forward into the retina. This is called choroidal neovascularisation (CNV). Typically CNV occurs in the central part of the retina which is called the macula. The most precious part of the macula is the fovea which lies in the very centre of the macula and is responsible for central fine vision.

CNV causes damage by leaking fluid and blood into the retina which disrupts the normal architecture of photoreceptors. Eventually these blood vessels mature into a fibrous scar at which stage no intervention to halt or reverse the process is possible. Thus choroidal neovascularisation and the resultant disciform scar typically result in complete loss of central vision and legal blindness. This process once established may progress rapidly over days or weeks. Therefore prompt referral of patients and urgent intervention by ophthalmologists is crucial for the treatment of wet AMD. The economic cost of blindness because of wet AMD to the United Kingdom is high. Recent estimates suggest it could be over £300 million pounds per annum (Pfizer Burden of Illness study, accepted Archives of Ophthalmology).

Current treatment of "wet AMD" includes thermal photocoagulation of CNV if the area of CNV is outside the foveal region of the eye. In practice patients rarely present with extra-foveal CNV as they are unaware of the problem until the CNV is sub-foveal and affecting central vision. CNV is much more common in the central macula region of the eye rather than away from the fovea and so extra-foveal CNV is relatively rare anyway. To put this in context, in my practice I see around 500 patients with wet AMD per year but I typically only treat 2-3 patients with extra-foveal thermal laser. This emphasises that only a very small proportion of people with wet AMD can be helped with thermal photocoagulation.

For the last two years we have been able to treat patients with "classic or predominantly classic" sub-foveal CNV with a type of laser treatment called photodynamic therapy (PDT). This was a significant step forward from thermal photocoagulation of CNV because it allowed treatment to be applied if the CNV was sub-foveal which was the reality in the majority of cases. Determining whether a CNV membrane was classic or predominantly classic requires considerable skill in interpretation of fluorescein angiograms and so PDT centres were set up in approximately 50 regional centres. This has probably reduced costs but there have been variations in patient access to these centres. Certainly some patients have not benefited from this treatment because of their reluctance to travel to PDT centres. In

our hospital there has been a wide variation in patient utilisation, with patients closest to our Unit being more likely to present for treatment. It is important to remember that wet AMD affects elderly, visually impaired patients and so travel for treatment is an important consideration in planning care pathways.

Unfortunately it is only the minority of patients with wet AMD who have classic or predominantly classic CNV (around 10-20%). Therefore for the majority of patients with wet AMD there has still been no treatment to halt the process of disciform scarring from CNV. In addition, while the results from PDT for those offered treatment have been better than no treatment, (approximately 2/3 of patients show stabilisation of their impaired vision) they have not been spectacular. The majority of patients have continued to lose vision despite treatment and only a small minority (5%) have seen visual improvement. Therefore the majority of patients with wet AMD still remain visually impaired or legally blind despite the availability of PDT treatment on the NHS. Clearly much still needs to be done to improve treatment for patients with wet AMD.

In this context of current treatments for wet AMD, NICE is now considering two novel treatments for wet AMD. These are the drugs pegaptanib and ranibizumab. The main difference between pegaptanib and ranibizumab is that ranibizumab is a pan VEGF-A monoclonal antibody blocker whereas pegaptanib is an RNA aptamer directed against vascular endothelial growth factor (VEGF)-165, the VEGF isoform primarily responsible for pathological ocular neovascularisation and vascular permeability.

Pegaptanib was the first agent to report clinical trial data. Its results were significantly better than placebo and importantly it could be used in all sub-types of wet AMD (Gragoudas ES, Adamis AP, Cunningham ET, Jr., Feinsod M, Guyer DR, the VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for Neovascular Age-Related Macular Degeneration. The New England Journal of Medicine 2004;351:2805-2816).

The results from the clinical trials of ranibizumab have however been even more spectacular. Again ranibizumab has been shown to be effective in all forms of wet AMD, but even more impressively vision can be significantly improved. For example, in the Marina study, 33 % of patients gained 15 letters or more from baseline which was maintained for 24 months (Rosenfeld PJ, Brown DM, Heier JS et al. Ranibizumab for Neovascular Age-Related Macular Degeneration. The New England Journal of Medicine 2006;355:1419-1431). This is a highly significant result which has the potential to revolutionise the management of wet AMD. In terms of patient care it has the potential to rescue patients whose vision is at or near the level of legal blindness and enable them (in some cases) to drive again. This is a truly astounding development in our management of wet AMD.

Anti-VEGF agents therefore represent a major step forward in treating AMD, with outcomes that include significant improvement and preservation of sight. These outcomes have not been seen before with other treatments for wet AMD. They therefore represent the first ever treatment for AMD which can significantly rescue vision.

It is not clear yet whether pegaptanib and ranibizumab will completely replace PDT as a treatment for wet AMD or be used in combination with PDT. Current studies are investigating different combinations of anti-VEGF agents and PDT to devise optimal treatment protocols.

Of note there are significant resource implications of introducing pegaptanib and ranibizumab into the NHS. These drugs allow 100 % of patients with wet AMD to be offered treatment (not just the 10-20% offered treatment with PDT). In addition these patients require sequential intraocular injections initially on a 4 weekly basis in the case of ranibizumab, instead of the 3 monthly review protocol utilised in PDT laser treatment. Therefore NHS commissioners must budget for this in their development plans for anti-VEGF therapies for wet AMD.

Additional service costs will therefore include a significant increase in specialist retinal procedures, and facilities that ensure sterile and safe provision of drugs and intraocular injections. Between 1-2% of patients experience potentially serious adverse events, including endophthalmitis (severe internal eye infection), retinal and lens injuries, and other complications and these will result in additional costs to the NHS. Additional imaging resources such as optical coherent tomography and additional photographers may be needed as well as additional medical and nursing personnel to cope with the six fold increase in work load. This six fold increase is calculated by realising we are treating 80-90%

more patients on an ongoing basis for perhaps two years (rather than discharging those 80-90% who we cannot treat with PDT) and in addition seeing these patients three times more frequently than with PDT (4 weekly instead of 12 weekly). NHS commissioners will need to budget for all these additional costs (in addition to drug costs).

To summarise, anti-VEGF agents represent a significant development in the management of wet AMD. They offer sight saving treatment not available with any other current treatment modality. There will be significant economic savings from preventing people going blind and I believe these treatments should be implemented as soon as possible into the NHS. Significant resources will have to be provided to hospital eye services to cope with the increased workload.

In what setting should/could the technology be used?

There are several key steps in planning introduction of this service. Firstly clinicians need to be able to diagnose wet AMD and secondly to monitor the response to treatment. Current consensus is that diagnosis requires two retinal imaging technologies. These are fundus fluorescein angiography (FFA) and optical coherent tomography (OCT) imaging. FFA provides a dynamic evaluation of blood flow in the retina and so assesses how active a CNV membrane is. OCT assesses whether sub-retinal fluid and scar tissue is present but does not provide a dynamic evaluation of blood flow. Initially patients require FFA and OCT to confirm diagnosis and evaluate how much sub-retinal fluid is present. Response to treatment can be monitored by OCT where a decision to treat can be made if sub-retinal fluid is seen to recur. In some cases sub-retinal fluid becomes recalcitrant and in those cases FFA is useful to assess whether a CNV membrane is still active or whether residual sub-retinal fluid is loculated and the CNV is inactive.

Fluorescein angiography can cause anaphylaxis and so resuscitation services must be readily available. For this reason, and also because of the capital expenditure of providing FFA and OCT cameras, these imaging services are best placed in a hospital setting.

Secondly safe injection into the intra-vitreal space is a highly skilled procedure where a 1 mm error in the ocular injection site can cause either cataract or retinal detachment. Therefore this is a highly specialised service and should be carried out in a hospital eye department where resuscitation services are available and where ophthalmologists can safely inject these drugs repeatedly into patients' eyes. My opinion concurs with clinical guidelines devised by the Royal College of Ophthalmology (www.rcophth.ac.uk/docs/scientific/IVT_Inject_Guidelines_FINAL_for_website.pdf)

The advantages and disadvantages of the technology

The advantage of this technology is that it represents the first highly effective treatment for wet AMD which can save thousands of patients from becoming legally blind. The disadvantage is that it requires an intra-ocular operation and carries the risk of operative complications such as endophthalmitis. It requires multiple intra-ocular injections. However most patients even though elderly are very happy to have an intra-vitreal injection knowing it will stabilise or improve their sight.

The main challenge with this technology is that it will require a major reorganization of medical retinal services. Significant investment will be needed in technology to image the retina to assess when to stop or start treatment. This will require additional resources for OCT imaging and fluorescein angiography. Additional medical, nursing and photographic and administration personal will be needed to safely inject these drugs on a monthly basis to 100% of patients with wet AMD. I anticipate that as protocols mature the number of injection treatments will reduce. Trial data suggest the best results occur with three injections and after that vision stabilises but that repeated injections are necessary to maintain this improvement and stabilisation of vision. It may be that in the future, treatment duration may be reduced by the combination of an anti-VEGF agent and PDT. These protocols are evolving at present.

Implementation issues

Despite the challenges of implementing an anti-VEGF service I would strongly urge NICE not to delay implementation for more than the standard three months. My personal experience of trying to set up a PDT service for wet AMD was extremely frustrating. In that case PDT implementation was recommended within 6 months of the final NICE appraisal. In my area this merely delayed implementation of this service and commissioners only seriously considered funding the service as the 6 month deadline arrived. It took a further 3 months after the 6 month deadline before we had a fully funded service in Hampshire. Prior to this we had to approach individual patient's primary care trusts to request funding on a case by case basis. Patients literally went blind as we waited for approval to treat. Similarly in this situation commissioners typically will only pay for the drug cost and not the infrastructure costs. It is impossible to run an anti-VEGF service without infrastructure. Patients will go blind if they have to wait for approval for treatment on a case by case basis – typically this application process takes 4-6 weeks. By this stage the CNV will have converted to a disciform scar and treatment is no longer an option. Therefore the most equitable solution is for NICE to recommend full implementation within 3 months.

Also in view of the difficulties of some patients accessing treatment with PDT I believe treatment should be available in district general hospitals where hospital eye services can provide 1) ophthalmologists skilled in the provision of intra-vitreal injections and 2) adequate retinal imaging to assess when to stop / start treatment.

To summarise my personal statement:

1. Anti-VEGF agents represent a momentous step forward in the management of wet AMD.
2. The best results have been seen with ranibizumab.
3. Treatment with these agents should be implemented as soon as possible and our experience with PDT implementation suggests treatment implementation should not be delayed beyond 3 months.
4. NHS commissioners must provide resources for the considerable infrastructure needed to deliver an anti-VEGF service.
5. Unlike PDT, anti- VEGF treatments can be provided at District General Hospitals to improve access for all patients.
6. These treatments will significantly reduce the incidence of legal blindness in the UK. Their implementation costs should be more than offset by the reduction in economic burden resulting from blindness. They represent a much cheaper alternative than blindness due to wet AMD.