2010

Aggressive wet age-related macular degeneration

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Publication Details
This article was originally published as T. Cleary, "Aggressive wet age-related macular degeneration", Illuminate 1 10 (2010) 26-31.
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Abstract
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Disciplines
Arts and Humanities | Life Sciences | Medicine and Health Sciences | Social and Behavioral Sciences

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This journal article is available at Research Online: http://ro.uow.edu.au/hbspapers/127
Case Report of Aggressive Wet Age-related Macular Degeneration

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Aims
The purpose of this paper is to use a case study to illustrate an encounter with aggressive wet Age-related Macular Degeneration (wet AMD) and discuss clinical interpretation issues related to primary care optometry.

Key words
Macular degeneration, clinical interpretation, undone science.

Introduction
Age-related Macular Degeneration (AMD) is a major cause of visual impairment in Australia and the developed world (AIHW, 2005). Robyn Guymer describes how in AMD “Vision is lost either from a slow atrophic process (dry AMD) or from a much more rapid and destructive process of choroidal neovascularisation (wet AMD)” (2007: p 276).

Following a recent scientific breakthrough, wet AMD can now be treated with anti-VEGF drugs that can halt the growth of new blood vessels and retain central eye sight (Fong et al., 2008, Upton, 2009). Originally developed as a novel cancer treatment to block the action of Vascular Endothelial Growth Factor (VEGF); these anti-angiogenesis drugs were found to limit the production of new blood vessels in fast growing tumours and coincidentally halt the choroidal neovascularisation process in wet AMD.

Angiogenesis is a term used to describe the growth of new blood vessels, and goes back to the work of surgeon John Hunter in 1787 (Hess, 2006). Angiogenesis was identified by Judah Folkman (1971) as a potential method of fighting cancer by attacking its blood supply. Following Folkman’s work, a broader study on growth factor at Genentech identified VEGF factors identical to the tumor VEGF factors discovered earlier (Leung et al., 1989, Folkman et al., 1971).

This led to the exciting development of bevacizumab or Avastin, a mouse derived full-length humanized anti-VEGF monoclonal antibody, and was to be used to treat metastatic colorectal cancer (Hurwitz and Kabbinavar, 2005). Later bevacizumab (Avastin) was used for other applications and Michaels et al.(2005) and Rosenfeld et al.(2005) trialled it on patients in the hope of controlling wet AMD firstly with systemic application and then intravitreal injections (as cited by Krebs et al., 2009).

Eventually four long term trials of the related drug ranibizumab or Lucentis were conducted and published.

“Lucentis® (ranibizumab, formerly RhuFab V2) is a modified fragment of an anti-VEGF antibody (Avastin® that binds and inhibits all VEGF isoforms (Krzystolik et al., 2002). Initial studies with the full length antibody suggested that it did not penetrate the retina when injected into the vitreous cavity (Mordenti, 1999). However, the Fab fragment passed easily through the retina to reach the target (subretinal) space. An affinity maturation process was applied to increase the binding affinity to VEGF 140-fold, and Lucentis® was moved into clinical studies. The results from four large randomized clinical trials have been reported to date. (CATT, 2008: p 1.5)”
The CATT Study Group are currently investigating *Lucentis* and *Avastin* in head-to-head trials and they have noted that initial reports of poor retinal penetration of the full length antibody were challenged by later studies (CATT, 2008: p 1.7): “In addition, when Avastin® was injected into the vitreous of rabbits, it showed full penetration of the retina (Shahar, 2006; Feiner, 2006; Schraemeyer, ARVO 2006).” In any case the drug *Lucentis®* received approval (US BL 125156) for treatment of neovascular AMD on June 30, 2006, but *Avastin* requires further research, clinical trials and licensing application by Genentech to receive FDA approval (Raftery et al., 2007).

It is commonly known that wet AMD has a large impact on an individual’s quality of life and it comes at a large cost to our ailing health system. Many studies simply use economic and epidemiological data to argue the relative benefits of funding research, and the designated subsidy of new treatment and diagnostic methods of wet AMD. However, when looking at someone’s health, it must not be seen as purely a numbers game. Studies that focus on using preventative techniques to reduce the social impact of AMD, and research in low vision and rehabilitation of visual function in those people affected by AMD also have an equally important role to play in developing modern approach to this disabling condition (for a global perspective on Low Vision see: Herse, 2008).

**Case Report of Aggressive Age-related Macular Degeneration**

Mr SL is now in his eighties and is still quite active; he enjoys travelling and also researching local coal mining history. He reports: “This involves field visits, interviewing older people, research at Wollongong Library and the University, reading many books and writing. It is imperative that I retain at least partial eyesight to continue with this work." He also suffers from chronic kidney disease and is on dialysis and exchange bags four times daily: “This condition has put a stop to major activities such as flying and travelling long distances by bus or train. Holidays are therefore curtailed.” Finally, he has severe arthritis in both knees which makes walking difficult: “Life would be made far more difficult if I could no longer drive.”

**Part One: Initial Presentation of Macular Disease**

In July 2005 Mr SL presented for routine eye examination. He has been a long time client of this practice.

He had slight cortical cataracts, pre-macular fibrosis in the right eye, and slight macular pigment changes in the left eye.

BCVA: R 6/7 L 6/7

In August 2005 a review with a local ophthalmologist confirmed these findings.

In September 2005, SL returned because vision in the right eye felt dim, and a slight Amsler grid defect was noted but VA’s and fundus appeared unchanged. He was asked to monitor central vision with an Amsler grid and return if he noted problems.

In November 2005, only 2 months later the right eye changed dramatically.

BCVA: R 6/90 L 6/7

(a round grey blob was reported in the centre of vision of the RE with no distortion on the Amsler grid)
Prompt referral to retinal specialist confirmed a right subfoveal choroidal neovascular membrane. At this time classic subfoveal new vessels were treated with Visudyne; with an aim to reduce the amount of vision lost but with little hope of regaining any functional visual acuity in the eye (see: Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) Study Group, 2001). Later in Mr SL's treatment the anti-VEGF drug Avastin became available, in April 2006. Treatment with Avastin intravitreal injections reduced the amount of macular edema and the size of the subfoveal vascular network. Despite this, there was no improvement with vision from either treatment; Mr SL's right eye developed a macular scar resulting in a central scotoma or blind spot (see figure 1.1).

**Part Two: Establishing Long Term approach for Monitoring for Macular Disease**

In monitoring Mr SL, of major concern was the length of time he had waited before returning for a recheck of the right eye despite the huge drop in VA. A misinterpretation of the disease process could well have affected his long term prognosis.

As his vision worsened Mr SL thought it was an expected progression of the previously diagnosed pre-macular change. He also lacked an understanding on how to use the Amsler chart and the importance of the test. Instead of looking at the *amount of distortion, intensity of blur*, or more importantly the *area affected by the blur* he was just looking out for ‘distortions’ not aware lines could completely go missing.

Subsequently, emphasis was placed on correct instructions, so that he could at least monitor his relatively healthy left eye. In part this was easier now as Mr SL only had the central vision in the left eye remaining and so even a slight change in central vision was bound to be more noticeable.

Besides some slight nuclear sclerosis cataract changes there was no major pathological issues in the left eye threatening sight. Despite this because of underlying pigment changes, even without the presence of drusen, it was considered quite possible that the left eye would also become affected by aggressive Macular disease at some point.

The dynamic of clinical referral for wet AMD had changed dramatically over this period of time with the introduction of OCT imaging and potential of patients receiving anti-VEGF drug therapy. This was some what of a motivating factor as it was clear that Avastin had a clinical effect of reducing the activity of the subfoveal new vessel with Mr SL’s right eye. If a new vessel was found growing in the left eye it was hoped that Mr SL’s central vision could be saved by using the drug to stop the blood vessel growing.

Over several subsequent visits to the optometrist and ophthalmologist Mr SL’s best correct VA in the left eye deteriorated to 6/9 mainly due to advancing cataract. Then in June 2007 Mr SL made an appointment with the optometrist after “observing line distortion on the Amsler Chart.” Best correction in the left eye was now 6/18 but unstable and patchy. The macular view was poor even with dilation due to cataract changes obscuring the view, despite this a small haemorrhage and minimal macular edema was detected (see also figure 1.1 and 1.2 taken later after resolution of most of the new vessel signs). Urgent referral to a retinal specialist in Sydney was arranged; being a Friday before the June long weekend, Mr SL was seen by the specialist that afternoon. The retinal specialist confirmed Mr SL had neovascular changes in the left eye. He more specifically diagnosed Mr SL’s eye disease as an aggressive variant of Age-related Macular Degeneration called retinal angiomatous proliferation or RAP (Yannuzzi et al., 2001).
Part Three: Long term Medical retinal treatment and monitoring of vision

As previously discussed since the last time Mr SL had a CNV (in the right eye) two major technological advances in diagnosis and treatment had become more readily available; the Optical Coherence Tomography scanning (OCT) and anti-VEGF therapy. After fluorescein and OCT examination the retinal specialist confirmed the RAP variant of AMD (retinal angiomatous proliferation), and, on that same Friday afternoon an intra-vitreal injection of Avastin was given (Meyerle et al., 2007). This time the new blood vessel was found in time for the drug to be effective in restoring clarity to central vision. The central vision of the left eye recovered to 6/12 with slight distortion to the lower left of centre on the Amsler grid. Monthly injections of Lucentis have been used to stabilize the AMD since it became available under PBS.
Mr SL continues his research in local history and takes turns driving when he and his wife travel; they have recently been down to Eden, about 1000km away, in the car on a road trip. The burden of ongoing treatment is something that has changed Mr SL’s life even though the treatment effectively maintains his remaining central vision. Thankfully local eye specialists have begun to provide medical retinal treatments and advanced retinal diagnosis and imaging. Mr SL attends their rooms to have regular injections of Lucentis and to check for the stability of the macular in order to retain the central vision of his left eye. Figure 1.1(below): Retinal photo of Mr SL’s right eye (photo courtesy OPSM Wollongong).

Figure 1.2(below): Retinal photo Mr SL’s left eye (photo courtesy OPSM Wollongong). Two months after beginning Anti-VEGF drug therapy the macular area had stabilised.
Discussion

Timely referral is essential for CNV, especially for this aggressive variant. It is hoped that this case study will increase awareness amongst optometrists and the people they encounter in their primary care role. Patients and eye care professionals need to be aware that with or without anti-VEGF therapy, whether *Avastin* or *Lucentis*, early detection and timely management of AMD is essential. This involves clearly communicating with patients the disease process to help to guard against poor outcomes due to a lack of understanding of the signs or symptoms of the disease.

Patients, Optometrists, Ophthalmologists and the broader health system are on the front line together against this blinding disease. We all have an important role to play in patient management, but whenever dealing with the disease, we should not forget that we are also dealing with the quality of a person's life.

Medical retinal diagnosis and treatment has become more effective over the last five years but AMD is such a huge problem for people in the community that much more needs to be done to mitigate the impact of this blinding disease. It has long been recognised that some research priorities gain precedence over others for political and economic rather than clinically derived reasons (Richards, 1991). More specifically David Hess describes science that is left incomplete or under-resourced for political and economic reasons as “the problem of undone science”. According to Hess this undone science can be the result of a systemic effort by elites who put structures in place that keeps research from being done (2007: p 23). As Guymer points out in the March 2007 Medical Journal of Australia (just 3 months before Mr SL’s left eye was affected by AMD):

“No prospective randomised studies comparing ranibizumab (Lucentis) and bevacizumab (Avastin) have taken place, although there are plans for such a trial through the US National Eye Institute. Until the results of such a comparative trial are forthcoming, government and the community face a dilemma of whether to approve and subsidise the well studied but expensive drug ranibizumab or delay that decision and therefore condone the off-label use of a drug (Avastin) that has not been submitted to the rigours of a randomised clinical trial nor studies to the extent that we expect before a new drug is introduced.(Guymer, 2007)”

Mr SL’s clinical experience has highlighted the importance of addressing current issues related to undone science of medical retina research into angiogenesis occurring in AMD and other ocular disease (for example CNV secondary to Ocular Toxoplasmosis: Chan, 2008). The major undone science issue of the yet to be completed *Avastin-Lucentis* head to head trial (which is due to be completed in 2011) captures the key elements of the challenges involved in reconstructing and reforming medical science. Mr SL’s plight in obtaining emergency and ongoing treatment for his aggressive wet AMD is intimately related to the controversy surrounding this area (Brown et al., 2009, Rosenfeld et al., 2006).

It is important to take time to remember that the principal endeavour of primary care and all health care is to take the meaning surrounding health and illness and introduce it thoughtfully within the space of the everyday.
References


