Editorial

AMD - Current Standard of Care and the Pakistani Perspective

The millennium started with a gift for the evergrowing blind population of the world, especially in the developed world, where age-related macular degeneration (AMD) ranked as the leading cause of unpreventable blindness. Millions were saved from going permanently blind with the onset of new therapies aimed towards preserving and improving vision in these patients.

For many years the retina specialists were unable to treat choroidal neovascularization (CNV) in AMD with good visual results. In the early 90's some success was reported with laser photocoagulation treatment of small classic CNV lesions. But ultimately the concept of foveal photocoagulation which was recommended by the MPS subfoveal study was rejected as the long term results were hopeless.

Alternate approaches in the mid and late 90 included submacular surgery with macular translocation and radiotherapy. Very little functional benefit was accomplished in the majority of these patients while subjecting them to a high rate of potential adverse complications. The same was true for TTT (Transpupillary Thermotherapy), which never came up to the expectations.

In 2000, the approval of verteporfin (Visudyne) Photodynamic therapy (PDT) heralded a new era in the treatment of CNV. Visudyne was initially approved only for classic CNV where there was a clear cut treatment benefit; but in reality this treatment prevented vision loss and typically did not improve vision in the majority.

PDT was the standard of care for neovascular AMD in the period ranging from 2000 to 2005. At the same time pharmacologic therapy with antivascular endothelial growth factor (VEGF) agents was undergoing development. It was demonstrated that VEGF was an important mediator of neovascularization in human eyes with CNV and AMD. The first commercially available anti VEGF agent for intraocular use was Pegaptanib (Macugen) which became available in early 2005. It stabilized the visual status but substantial visual improvement was uncommon.

In the middle of this decade intravitreal injections of Avastin (bevacizumab) and later Ranibizumab (Lucentis) emerged as a superior treatment. FDA approval of Lucentis occurred in July 2006. Lucentis is a drug derived from Avastin and it has been demonstrated to be the first and only drug for CNV in AMD that results in substantial and clinically relevant visual improvement

Avastin, a drug originally approved for colorectal carcinoma, has become widely adopted because in addition to potentially better visual results than either Macugen or PDT, the drug is also much cheaper.

At this point, jury is still out about which of the two contenders, Avastin or Lucentis, is the best. Both induce regression of CNV and lead to significant improvement in vision. Both drugs are FDA approved but only one is labeled for intravitreal administration. Lucentis is supported by clinical trials, and the other by many uncontrolled studies as well as virtual unanimity among retinal specialists. Lucentis is smaller molecule with a shorter half-life and is approximately 100 times more expensive than Avastin. Age Related Macular Degeneration Treatments Trials (CATT), a multi-centre randomised clinical trial will assess the relative safety and efficacy of two treatments for subfoveal CNV. It is being conducted in 47 clinical centres across the US. This study will determine if Avastin is similar to Lucentis when given on a monthly basis.

The drawback of Avastin or Lucentis is that they do not permanently close the CNV. Most clinicians give three injections of Avastin or Lucenits at monthly or every six week intervals. They then watch the patients and give additional injections on an as needed basis. Some patients however, need injections every month. Patients get tired of these injections and each one of them has a small risk of endophthalmitis. Therefore a treatment for AMD that involves fewer or no injections is needed. Irrespective of which form of treatment we use, we must understand that CNV in AMD is a chronic disease that will require ongoing treatment, currently with injections. Given our current available treatments, we now know when to treat;

however, we still need better understanding of when to continue or discontinue treating to enhance safety and efficacy and to reduce costs.

Larger randomized clinical trials are currently underway, including trials combining PDT/VEGF inhibitor (LUV Trial, DENALI, MONT BLANC), PDT/ VEGF inhibitor/corticosteroid (RADICAL, TAPER), and PDT/corticosteroid (VERITAS).

Ongoing research is exploring other complementary or alternative anti-VEGF strategies. The VEGF trap and gene suppression or small interfering RNA (siRNA) drugs for reducing VEGF production or blocking VEGF receptors are attractive concepts for development as mono- or combined forms of therapy. These methods of treatment are still in developing stages. While rehabilitation of end stage AMD patients has classically involved the use of Low Visual Aids, all eyes are set on the development and ultimate availability of the retinal chip (the proverbial bionic eye) to help patients who have already gone to the scarring stage.

While research from the west keep coming up with promises of newer and better treatments, we in Pakistan, have been using PDT and anti VEGF drugs, as mono-therapy and combination, with varying degrees of success. Our initial experience of PDT monotherapy from 2001 to 2005 exhibited better outcomes than our international counterparts. This was due to the fact that we were treating more classic lesions that are expected to respond better. We joined the anti-VEGF bandwagon with the advent of Macugen and treated few patients with results similar to PDT i.e. stability of the lesions and not much improvement in the visual acuity. It was only after the advent of Avastin and Lucentis that we witnessed significant improvement in majority of the patients. The choice of the Anti-VEGF has largely depended on the financial status of the patients. Lucentis is the drug of choice if financial constraints aren't a consideration and Avastin use is now a knee jerk reflex in the converse situation

We in Pakistan have witnessed that although we are developing country the behaviour of our urban population is similar to that of the developed world. AMD is on the rise with increasing longevity of older population. We are also are observing an earlier onset of disease in our population.

Our Government's role should be to improve the facilities for AMD patients as there are no retinal centres and patients don't know where to go and to ensure the provision of treatment especially considering Avastin is not so expensive (around Rs. 300 per injection). Doctors also need to be properly trained for these procedures. If proper protocols are not being followed, there is a likelihood of encountering serious sight and eye threatening complications. International literature shows unanimously that the complication and side effects reported were directly correlated with the technique rather than the type of injection. It is the responsibility of ophthalmic community to promote and monitor proper usage of these intravitreal injections.

Dr. Azam Ali