REVIEW ARTICLE

Recent Advances in the Management of Age-Related Macular Degeneration

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Age-related macular degeneration (AMD) is a degenerative disease associated with aging that affects the macula and causes gradual loss of central vision. The disease is now a leading cause of blindness in the developed world in persons aged over 65 years (1).Treatment modalities include:

- *Modification of risk factors*
- *Dietary supplementation*
- *Laser photocoagulation with argon-blue or krypton-red lasers*
- *Photodynamic therapy with verteporfin*
- *Transpupillary thermo-therapy with infra red light*
- *Antiangiogenic drugs like -*
- *Steroids (e.g. intravitreal triamcinolone acetate and anecortave acetate)*
- *Anti-VEGF (vascular endothelial growth factor) drugs*

Introduction of anti-VEGF drugs has revolutionised the treatment of exudative AMD. It is now a well-known fact that CNVM (choroidal neovascular membrane) harbours VEGF receptors that promote neovascularization. Thus, a drug that blocks these receptors can prevent angiogenesis. Currently, three anti-VEGFs are available for treatment:

- *Pegaptanib sodium*
- *Bevacizumab*
- *Ranibizumab*

Pegaptanib sodium : is an aptamer that specifically binds with VEGF 165 isoform in humans. VISION (VEGF Inhibition Study In Ocular Neovascularization) has demonstrated the efficacy and safety of the drug. The drug appears to be safer than the other two anti-VEGF agents as it has selective blockage action and therefore minimal systemic effects particularly cardiovascular (2).

Bevacizumab : It is a full length recombinant humanized monoclonal antibody directed against all VEGF isoforms. Encouraging results in the form of stable or improed visual acuity, decrease in FA leakage and OCT findings have led to extensive off-label use of drug and multiple trials have ever since proved its efficacy in improving macular odema. When used to treat colon cancer, the higher and frequent doses of bevacizumab are found to cause thrombembolic and cardiovascular events, gastrointestinal perforation, hemorrhage and nephrotic syndrome (3).

Ranibizumab : is an antigen binding fragment of the recombinant, humanized mouse monoclonal VEGF antibody. Although Avastin has not got FDA approval, it is more extensively used then Lucentis because of the huge cost difference. While one vial (0.15 ml) of Lucentis costs around rupees 58,000 in India, the price of Avastin is rupees 37,000 for a 4 ml vial, i.e. rupees 3,000 per injection of 0.15 ml.

The MARINA (Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular AMD) (4) and ANCHOR (Anti-VEGF Antibody for the treatment of predominantly Classic Chordial neovascularization in AMD) (5) trials have evaluated the drug in occult and classic CNVMs, respectively, while FOCUS (RhuFab V2 Ocular treatment Combining the Use of visudyne to evaluate Safety) (6) trial has evaluated the role of combination therapy of ranibizumab + PDT in predominantly classic lesions.

Advances in the Treatment of Dry AMD

AREDS (Age-Related Eye Disease Study): The results of AREDS demonstrated a statistically significant benefit for the combination of high-dose antioxidant vitamins and zinc in providing a moderate reduction in the risk of developing advanced age-related macular degeneration (AMD) over a median of 6.3 years of follow-up in persons at high risk (7).The formulations included:

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- *Vitamin C (500 mg)*
- *Vitamin E (400 IU)*
- *beta-carotene (15 mg)*
- *Zinc (80 mg of zinc oxide); and*
- *Copper (2 mg of cupric oxide)*

Age-Related Eye Disease Study 2 (AREDS 2) result awaited (8).

The objectives of AREDS 2 are listed as follows:

1. To evaluate the effect of the two dietary xanthophylls (10 mg lutein and 2 mg zeaxanthin that accumulate in macula and two omega-3 long-chain polyunsaturated fatty acids (LCPUFAs), docosahezaenoic acid and eicosapentaenoic acid (350 mg DHA and 650 mg E PA as 2 soft-gel capsule), on progression to advanced age-related macular degeneration (AMD) and/or moderate vision loss in people at moderate to high risk for progression.

2. To evaluate the effects of eliminating beta-carotene from the original AREDS formulation on the development and progression of AMD.

3. To evaluate the effects of reducing zinc in the original AREDS formulation on the development and progression of AMD.

4. To contribute data for validation of the photographic AMD scales developed from the AREDS.

Fenretinide in Dry AMD

It is being studied for patients in geographic atrophy. It is an oral vitamin A binding protein antagonist. It haults the accumulation of retinol (vitamin A) toxins through affinity for retinol binding protein. One of the hallmark of dry macular degeneration is the accumulation of lipofuscin that is responsible for drusen formation and geographic atrophy. The hope is that fenretinide will block the process that creates this lipofuscin and have a positive effect on drusen and geographic atrophy.

CNTF in Dry AMD

Ciliary neurotrophic factor (CNTF) is a "neuroprotective" agent and effects apoptosis. The eyes receiving the high-dose showed a change in the total macular volume and increase in retinal thickness.

Copaxone (glatiramer acetate)

Macular degeneration, Alzheimer's disease and multiple sclerosis - all involve inflammation and formation of deposits - plaque in the brain in case of Alzheimer's, and drusen in the retina in case of AMD.Copaxone is being investigated as a treatment for all three diseases. It is already used to treat multiple sclerosis. Studies have shown that eyes treated with copaxone showed a reduction in drusen area of over 53% after 12 weeks.

Complement C5aR inhibition

C5aR has been found localized in drusen and on the edges of geographic atrophy. Pre-clinical studies have suggested that blocking C5aR could be useful in stopping wet macular degeneration. Studies are underway.

Advances in treatment of Wet AMD

CATT (Comparison of Age-related macular degeneration Treatment Trials: Leucentis-Avastin Trial) - was launched in 2008 to compare Leucentis and Avastin for treatment of wet AMD. Changes in visual acuity served as the primary outcome measure for CATT. It was seen that visual acuity improvement was virtually identical for either drug when given monthly (9, 10).

Epimacular brachytherapy

Epi-Rad 90 ophthalmic system: This system delivers radiation to the eye by inserting a probe directed to the macula for about 4 minutes after a vitrectomy is performed. The collateral radiation delivery achieved is 0.56 Gy to lens and 2.4 Gy to the optic nerve. With strontium 90, the targeted energy is delivered to an area up to 3 mm in depth and up to 5.4 mm in diameter. The radiation destroys the abnormal blood vessels to stop the progressing wet macular degeneration vision loss. This, when combined with anti-VEGFs agents may provide a effective alternative for patients with neovascular AMD (11).

VEGF trap

A new experimental antiangiogenic drug, called VEGF Trap-Eye is being tested for its ability for beneficial role over current therapies. VEGF trap is a fusion protein of key domains from human VEGF receptors level 2 with a human IgG Fc portion. VEGF Trap-Eye is a protein that binds to and inactivates a growth factor called VEGF (vascular endothelial growth factor) that stimulate blood vessel growth in AMD. Inhibiting these blood vessels reduces vision loss (7).

Immunomodulation in AMD

It is hypothesized that the underlying mechanism that leads to choroidal neovasularization (CNV) is similar to those at play in atherosclerosis. Complement and macrophages play a role. Hence, new immunomodulatory agents directed against specific parts of the immune system could be effective. Sirolimus administered via sub-conjuctival injections along with the anti VEGFs is an alternative under study. Other drugs under study are

infliximab (intravenous) and daclizumab (intravenous) (12).

Intravitreal POT-4 therapy

Unrestrained complement activation has been recently recognised as one of key factors in the pathogenesis of AMD and it has a curcial role in the development of CNV as well. Study for intravitreal complement inhibitor (POT-4) therapy in AMD patients with subfoveal CNV as a single intravitreal injection is under progress.

Gene therapy in Wet AMD

AAV2-sFLT01: This experimental drug uses a virus to transfer a gene into cell within the eye. This gene codes for a protein that will inhibit the growth of abnormal blood vessels under the retina. The study is ongoing and results awaited.

Surgery

Submacular surgery has not been shown to be an effective treatment for a lesion that is predominantly CNVM in Submacular Surgery Trial (SST) (13). Another option for submacular hemorrhage is intravitreal injection of tissue plasminogen activator (25/μg) with intraocular gas injection followed by prone positioning in the post-operative period.

Macular rotation surgery is an option for patients with recent onset subfoveal CNVM. This is especially suitable in cases where the distance between the inferior border of CNVM and FAZ is less than 1000μ.

Other treatment options available are: radiation, proton therapy, interferon 2a, thalidomide, RPE transplantation, stem cell therapy, rheophoresis (alters the blood flow characteristics and eliminates high molecular weight proteins from blood - this improves microcirculation and increases supply of nutrients to retinal cells).

Though many options are available for AMD management, most are in various stages of clinical trials and need further research. Anti-VEGFs and photodynamic therapy with verteporfin are leading the race for being the best alternatives available.

References

1. Mitchel P, Smith W, Altebos K, *et al*. Prevalence of age-related maculopathy in Australia: The Blue Mountain Study. *Ophthalmol* 1995; 102: 1450-60.
2. Gragondas ES, Adamis AP, Cunningham ET Jr, *et al*. VEGF inhibition study in Ocular Neovascularization Clinical Trial Group. Pegaptamib for neovascular age-related macula degeneration. *N Engl J Med* 2004; 351: 2805-16.
3. Dodgostar H, Waheed N. The evolving role of vascular endothelial growth factor inhibitors in the treatment of neovascular age-related macular degeneration. *Eye* 2008; 22: 761-67.
4. Rosenfeld PJ, Brown DM, Heier JS, *et al.* MARINA Study Group. Ranibizumab for neovascular age-related macular degneration. *N Engl J Med* 2006; 355: 1419-31.
5. Brown DM, Kaiser PK, Michaels M, *et al*. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; 355: 1432-44.
6. Heier JS, Boyer DS, Ciulla TA, *et al*. FOCUS Study Group. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration: 1 year results. *Arch Ophthalmol* 2006; 124: 1532-42.
7. Brown DM, Heier JS, Ciulla T, *et al*. CLEAR-IT2 Investigators. Primary endpoint results of a phase II study of vascular endothelial growth factor trap-eye in wet age-related macular degeneration. *Ophthalmol* 2011; 118(6): 1089-97.
8. Weigert G, Kaya S, Pemp B, *et al*. Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2011; 52(11): 8174-78.
9. The CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011; 364: 1897-908.
10. Davis J, Olsen TW, Stewart M, *et al.* How the comparison of age-related macular degeneration treatments trial results will impact clinical care. *Am J Ophthalmol* 2011; 152(4): 509-14.
11. Avila MP, Farah ME, Santosh A, *et al.* Three-year safety and visual acuity results of epimacular 90strontium/ 90yttrium brachytherapy with bevacizumab for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2011 32(1):10-8.
12. Stephenson J. Cancer drug offer effective, cheaper option for AMD. *JAMA* 2011; 305(2): 2053-54.
13. Submacular Surgery Trials (SST) Research Group. Surgery for subfoveal choroidal neovascularization of age-related macular degeneration: ophthalmic findings. Report 11. *Ophthalmology* 2004; 111;1967-80.