EMERGING THERAPIES IN THE MANAGEMENT OF ARMD

Changing paradigms :

Our understanding of age related macular degeneration has grown over the years, from the fluorescein angiography studies of Gass and Norton in the 1960's, that demonstrated choroidal neovascularization as the cause of visual loss in this disease. The thermal laser modality was proven to be useful to thermally obliterate the choroidal new vessels, obviously outside the FAZ (foveal avascular zone) a fact that was validated by the first MPS – macular photocoagulation study published over 20 years ago in 1982. However CNV recurred in 40% patients treated with thermal laser at the end of 1 year in 55% patients in 5 years(1).

Recurrences invariably left the patient with poorer and poorer vision. Sometimes further retreatments led to a situation, anecdotally referred to as "no macula, no macular degeneration"

PDT with Verteporfin since 2000 marked a watershed zone in our understanding and management of choroidal new vessels. For the first time a non thermal laser was used to activate verteporfin resulting in damage to the neovascular endothelium causing vessel occlusion. It is now possible to expect stabilization or even improvement in carefully selected patients. It is important to understand that preservation of retinal tissue and function is greater in the absence of thermal injury. While damage from thermal effects can be reduced by techniques such as TTT (Transpupillary thermo therapy) experts feel these are unlikely to be able to compete visually with drug based, photo receptor friendly modalities.

So while PDT remains the standard for predominately classic CNV and occult lesions with small size / poor V/A the search continues for newer modalities some of which will be available to patients in the coming year or two. Needless to emphasize, any future modalities will need to keep the verteporfin treatment trials as a "benchmark" to compare their short and long-term efficacy.

It is important to concede that the major focus of research is the treatment of Wet ARMD; the dry form is still largely untreatable.

Present role of Surgical treatments:

Surgical treatment is in the process of sorting out some major roadblocks. The surgical treatment has evolved along two models. The first involves translocation of the fovea from the area overlying the CNV to an adjacent normal area-the process being called macular translocation. This can be achieved by a 360 degree retinotomy or a limited translocation by outpouching or imbrication. The fairly radical surgery for what is mainly a central vision loss has been the problem with these procedures.

The second approach was to remove the CNV by subretinal surgery. The visual results did not match the surgical feats as the RPE under the CNV was not healthy either. J.C Van Meurs and his group in Europe are using a patch

of RPE with choroid which is harvested from the mid periphery superiorly and is sandwiched between the retina and damaged RPE after removal of the CNV.

One must be pragmatic to say that surgical modalities have to still find their rightful place in the everyday safe management of ARMD.

Pharmacotherapy of CNV :

The search for newer drug based modalities stems from newer models at understanding the development of the CNV(2).

Direct and indirect evidence suggests that vascular endothelial growth factor (VEGF) is an important mediator in CNV. Two VEGF inhibitors rhuFab V2 (Lucentis from Novartis) and Pegaptanib Sodium (Macugen) are currently completing / completed phase III trials in the US. VEGF is a strong mediator of increased vascular permeability. Hence these agents predictably reduce permeability and macular edema and improve visual acuity. rhuFab V2 is a recombinant humanized antibody fragment that is designed to penetrate the ILM and reach the subretinal layers to specifically bind all 4 isoforms of VEGF to decrease vascular permeability and inhibit CNV formation. The Macugen is specific for recognizing VEGF165.Direct inhibition of proliferating CNV is also postulated. Durability of treatment has also been demonstrated with Lucentis by Puliafito.

The plasminogen activator is known to be an initiator of proteolysis of the extra cellular matrix aiding breakdown of existing vessel walls to create space for new blood vessels. Anecortave acetate (to be launched by Alcon labs) is an angiostatic steroid which induces plasminogen activator inhibitor (PAI)-1 m RNA which checks the plasminogen activator.

The VEGF inhibitors as also anecortave acetate have shown promising results while being evaluated against placebos with respect to stability or improvement in visual acuity and lesion growth

Another candidate anti-CNV agent which works by a completely different mechanism is Combretastatin A-4 phosphate. Animal models show its capacity to cause regression of established CNV, an advantage it enjoys over VEGF antagonists(3).

Since most of the investigational drugs have different mechanism of action a combined therapy may be the best course in future. Possibly Combretastatin to induce regression followed by VEGF antagonists to prevent recurrence.
In addition to mono therapy, phase III trials of anecortave acetate with PDT show great promise for reducing the retreatment (recurrence) with verteporfin. A fact especially useful is that anecortave acetate needs to be given sub tenons six monthly.

Routes of administration :

As of know Anti VEGF drugs will need to be given as an intravitreal injection probably repeated every 4-6 weeks.

Newer gene therapy approaches using a adenoviral vector to transfer large molecular weight endogenous ante-VEGF to transduce cells within the eye is a project being conducted by Genvec. The use of low molecular weight anti VEGF agents from subconjunctival implants is also being experimented(4). Ammosterol squalamine lactate as an IV infusion is being experimented by Gholam Peymans group in Mexico.

The age of retinal pharmacotherapy started with intravitreal steroids and anti virals and now shows promise for the management of ARMD. The development of drug delivery systems through sub conjunctival depot devices or through gene therapy will free the patient from repeated intravitreal injections.

References::

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