Age related macular degeneration is the leading cause of blindness among individuals 55yrs or older in developed countries. As the disease affects the central regions of the retina and choroid, central visual loss can ensue. Approximately 30 % of individuals who are aged 75 or older have some signs of maculopathy out of which 6 - 8 % have advanced AMD. By 2020 the prevalence of AMD is expected to be double of what is seen today.

The increasing prevalence of AMD has led many investigators to search for factors that could be modified to prevent the onset of or delay the natural course of AMD. Recent advances in clinical research have not only to a better understanding of the genetics and pathophysiology of age-related macular degeneration but also to new therapies designed to prevent and help treat it.

**PATHO PHYSIOLOGY**

With age, one change that occurs within the eye is the focal deposition of acellular, polymorphous debris between the retinal pigment epithelium and Bruch's membrane. These focal deposits, called drusen, are observed during funduscopic examination as pale, yellowish lesions and may be found in both the macula and peripheral retina (Fig 1). Drusen are categorized as small (<63 μm in diameter), medium (63 to 124 μm), or large (>124 μm) on the basis of studies that classified the grade of age-related macular degeneration.

On ophthalmoscopic examination, the diameter of large drusen is roughly equivalent to the caliber of a retinal vein coursing toward the optic disc. Drusen are also categorized as hard or soft on the basis of the appearance of their margins. Hard drusen have discrete margins; conversely, soft drusen generally have indistinct edges, are usually large, and can be confluent. The clinical hallmark and usually the first clinical finding of age-related macular degeneration is the presence of drusen. In most cases of age-related macular degeneration, damage to the retinal pigment epithelium and a chronic aberrant inflammatory response can lead to large areas of retinal atrophy (called geographic atrophy), the expression of angiogenic cytokines such as vascular endothelial growth factor (VEGF), or both. Abnormalities in collagen or elastin in Bruch’s membrane, the outer retina, or the choroid may predispose some people to this process. Consequently, choroidal neovascularization may be accompanied by increased vascular permeability and fragility. Choroidal neovascularization may extend anteriorly through breaks in Bruch’s membrane and lead to subretinal hemorrhage, fluid exudation, lipid deposition, detachment of the retinal pigment epithelium from the choroid, fibrotic scars, or a combination of these findings.

**CLASSIFICATION AND CLINICAL FEATURES**

According to the age-related eye disease study classification; early age-related macular degeneration is characterized by the presence of a few (<20) medium-size drusen or retinal pigment abnormalities. Intermediate age-related macular degeneration is characterized by at least one large drusen, numerous medium-sized drusen, or geographic atrophy that does not extend to the center of the macula. Advanced age-related macular degeneration can be either non-neovascular (dry, atrophic, or nonexudative) or neovascular (wet or exudative). Advanced nonneovascular age-related macular degeneration is characterized by drusen and geographic atrophy (Fig 2) extending to the center of the macula. Advanced neovascular age-related macular degeneration is characterized by choroidal neovascularization and its sequelae.

In the early course of the disease visual loss will be mild or even asymptomatic. Visual symptoms include blurred vision, visual scotomas, decreased contrast sensitivity, need for higher magnification and brighter light to read small print and altered dark adaptation. Over the course of months to years central or paracentral scotomas develop in these patients. In cases of neovascular age-related macular
Degeneration visual loss is usually abrupt and profound as a result of sub retinal fluid or hemorrhage secondary to choroidal neo vascularization. 80% of the cause of severe visual loss or legal blindness results from neo vascular AMD. However neo vascular AMD accounts for only 10 – 15 % of the prevalence of AMD. The risk of legal blindness in both eyes for a person with unilateral visual loss from neo vascular AMD may be approximately 12 % over a period of 5 yrs.\textsuperscript{10}

Non neovascular AMD is the most common form of AMD accounting for 80 – 90 % of overall cases. The clinical hallmarks of non neovascular AMD are drusens which are divided into hard, soft, crystalline, and cuticular or basal laminar according to their clinical appearance, histo pathological differences as well as fluorescense angiographic pattern. Drusens are localised deposits noted between the basement membrane of the retinal pigment epithelium and the Bruch’s membrane, associated RPE changes, and mild loss in visual acuity. The advanced form of non neo vascular AMD, termed geographic atrophy (Fig 2), is characterized by outer retinal and RPE atrophy with loss of chorio capillaries. Loss of central vision is usually due to RPE atrophy or geographic atrophy in non neovascular AMD. Early stage AMD (or early ARM) is defined as presence of soft drusen (63 micro meter) alone, RPE depigmentation alone, or a combination of distinct/indistinct drusen with pigment irregularities. Late stage AMD is defined as geographic atrophy (both central and non central), signs of neo vascular macular degeneration, or a combination of both.

Neo vascular AMD (Fig 4) which was first recognised as early as 1875 by Pagenstecher who termed this condition “chorioidoretinitis in regione maculae luteae” is characterised by major clinical features which include subretinal fluid, subretinal hemorrhage, sub RPE fluid (PED). Fig 3, sub RPE hemorrhage, RPE pigment alteration and hard exudates. Chronic neo vascular AMD is characterised mainly by presence of sub retinal fibrosis with or without other features of active exudation. The late manifestation of neo vascular AMD is a disciform scar (Fig 5) or geographic atrophy with or without subretinal fluid or subretinal blood. Sometimes the PED may rip resulting in an RPE rip which may be associated with active CNV. Spontaneous involution.
of CNV may manifest as any of the above findings with RPE alteration and or scar formation.

Polypoidal choroidal vasculopathy (PCV) has been classified as a form of CNV that may occur in patients. Yannuzzi and colleagues in their study determined the frequency and nature of PCV in patients suspected of harbouring neo vascular AMD. Clinical features include direct visualization of orange coloured polypl in the sub RPE space to PED’s which were commonly seen in PCV with signs of serous or serohemorrhagic RPE and or sensory detachment. This entity needs to be clinically distinguished from AMD in which ICG angiography plays a major role.

Retinal angiomatous proliferation (RAP) is another distinct type of neovascular AMD which is characterised by anomalous retinal vascular complex which is most commonly associated with retinal and sub retinal neo vascularisation. Yannuzzi and colleagues classified RAP as stage 1 which is described as a nodular mass of intra retinal neo vascularisation which originates from deep capillary plexus in the para macular area. There is usually one or more associated retinal vessels which either perfuse or drain the vascular complex with intra retinal hemorrhages and edema. Stage 2 is characterised by subretinal neo vascularisation, which involves both retinal and subretinal vascular proliferation with tangential growth and minimal horizontal extension. Other common signs include increased intra retinal edema, neuro sensory retinal detachment, serous PED and pre retinal and sub retinal hemorrhages. Stage 3 is defined by stage 2 findings plus the clear presence of CNV. While its natural history is not fully understood, it is thought to progress ultimately to a disciform scar. Prior to recognition of this entity, it was often mis diagnosed as occult CNV.

**RISK FACTORS**

Several clear risk factors for the development and progression of age-related macular degeneration have been established. The molecular pathways leading to age related macular degeneration remain to be elucidated. The retina and its pigmented epithelium are unique among body tissues in their constant exposure to light energy and high oxygen concentrations, both of which are potent sources of free radicals—therefore, it has been suggested that the cumulative effects of oxidative stress over a lifetime may be the initiating stimulus for macular degeneration. Concordant with this hypothesis are the findings of epidemiological studies, which show that cigarette smoking and a high lifetime exposure to sunlight are risk factors. One recent cross sectional population based study in the European Union found that people with low levels of antioxidants in their serum combined with high cumulative lifetime sunlight exposure had a two fold increased risk of developing late macular degeneration. More recently, consistent associations between the clinical spectrum of age related macular degeneration and polymorphisms in genes encoding proteins involved in immune regulation have been observed and provide additional insights into how this condition may develop. Carriage of at-risk alleles at multiple complement loci confer additive risks and, when combined with information on lifestyle factors such as smoking, can account for as much as 80% of the risk. Ocular risk factors associated with increased risk of CNV include 5 or more large sized drusen, confluent drusen, and hyperpigmentation. The simplified AREDS scale predicts the risk of CNV over the next 5 yrs and 10 yrs based upon the presence of drusen and pigment abnormalities in each eye.

**NATURAL HISTORY OF THE DISEASE**

Early macular degeneration can progress to late manifestations with sight loss in a proportion of people. The risk of progression is highly variable and depends on the severity and extent of the features of early macular degeneration. The age related eye diseases study has quantified this risk and showed that people with small drusen in both eyes have a very low risk of progression—between 0.4% and 3.0% over five years. However, if large drusen and pigmentary abnormalities are present in both eyes this risk increases to around 47.3%. Initially, geographic atrophy develops as focal areas of depigmentation. Eventually these coalesce or expand to involve the central macula causing progressive worsening of vision to legal blindness. Neovascular complications on the other hand have a more acute onset with sudden development of central blurring and distortion. Left untreated the area of neovascularisation expands rapidly and a large fibrous scar develops in the macula. A recent meta-analysis of data from several controlled clinical trials showed that within three years of the onset of neovascularization more than half of untreated eyes will have a level of vision of 20/200 (Snellen 6/60) or worse, which is within the WHO definition of severe visual impairment. The macular photocoagulation study (MPS) on extra foveal CNV showed loss of two or more lines in 50% of the affected eyes or 6 or more lines in 10% by 3 months after enrollment. Thus eyes with classic extra foveal CNV are at high risk for visual acuity loss. 13% of patients with juxtafoveal CNV in the natural history arm of MPS lost 6 or more lines in 10% by 3 months after enrollment. Thus eyes with classic extra foveal CNV are at high risk for visual acuity loss. 13% of patients with juxtafoveal CNV in the natural history arm of MPS lost 6 or more lines in visual acuity by 3 months after enrollment which increased to 58% by 36 months. The MPS sub foveal study is the largest study of the natural history of eyes with subfoveal CNV. In fact 77% of the patients lost 4 or more lines of visual acuity at 24 months and 64% lost 6 or more lines. When both eyes are affected with late stage age related macular degeneration sight can be markedly reduced and tasks that require visual discrimination, such as reading, driving, and recognizing faces become difficult.
DIAGNOSIS
Often diagnosis is incidental especially in the early course of the disease as presence of small area of geographic atrophy may not hamper visual acuity. In cases where there is advanced disease in one eye sometimes may be detected by chance. The diagnosis is usually evident on clinical examination and fundus photography. Stereoscopic fundus examination is the best method for examining a patient with AMD. Visual acuity estimation and amslers grid evaluation can also aid in diagnosing abnormalities.

FLUORESCIN ANGIOGRAPHY
Fluorescein angiogram (FA) has and continues to play an important role in managing patients with AMD. This investigation helped us in localising identifying and directing both laser and photo dynamic therapies as well as monitoring outcomes of treatment. With the advent of anti VEGF therapy the focus has shifted to where FA is useful in confirming the cause of exudative findings and identifying features that may limit visual benefits from the therapy. As newer therapeutic approaches are developed that may more selectively target the sub types and stages of neovascularisation, FA may once again be a critical tool in patient selection for these interventions.

INDOCYANINE GREEN ANGIOGRAPHY ICG
The role of ICGA in the treatment of AMD is in evolution. ICG Angiography has proven very useful in adding information to FA about lesion subtypes. The ability of ICG to identify subtypes of occult CNV, such as vascular PED, hotspots, plaques, and RCA allows targetting and sometimes effective therapy for these refractory types of CNV. It also helps us in differentiating polyoidal choroidal vasculopathy, retinal angiomatic proliferation, and recurrent choroidal neovascular membranes. Real time ICGA, wide angle ICGA and digital sub traction ICGA may improve our diagnostic ability in AMD.

OPTICAL COHERENCE TOMOGRAPHY(OCT)
OCT provides us with valuable information by giving in vivo cross sectional imaging of the affected macula. OCT can reproducibly track drusen morphology, volume and geographic atrophy. It is possible to directly visualise choroidal neovascular membranes and features of active neovascular tissue such as intra retinal fluid, sub retinal fluid or cystoid macular edema. High resolution and enhanced depth imaging helps us in finding new features such as ISOS abnormalities and choroidal vascular abnormalities. Qualitative and quantitative information provided by OCT may serve as the most important criteria in re treatment decisions.

AUTO FLUORESCENCE IMAGING
Fundus AF is a useful modality to image lipofuscin in retinal pigment epithelium cells and is a unique way to access RPE function in age related macular degeneration (AMD). Abnormal AF patterns are seen in patients with AMD. The normal homogenous fundus appearance is altered with areas of hyper or hypo AF. The international fundus auto fluorescence classification group (IFAC) described 8 distinct patterns of AF in early AMD namely normal pattern, minimal change pattern, focal increased pattern, patchy pattern, linear pattern, lace like pattern, reticular pattern, and speckled pattern. AF(automated imaging analysis) has been shown to be superior to other modalities in assessing the extent of atrophy. Increased AF especially at the edge of geographic atrophic area, may predict expansion. In neovascular AMD it helps us in assessing RPE health and consistently visualising RPE detachments. This is also a useful research tool to help validate and measure the efficacy of novel treatments for non neovascular AMD.

MICROPERIMETRY AND PSYCHOPHYSICAL TESTING
Microperimetry and a number of self monitoring tests including the time tested amslers chart are available for identifying AMD progression. Ongoing development of modern technologies allows detection of more subtle defects, quantitative analysis, and accurate follow up. Application of these tools in clinical practice and patient’s everyday life raises hope for earlier detection of disease progression and hereby better chances to preserve vision. Early detection and treatment of choroidal neovascularization is crucial for achieving better visual outcomes and avoiding permanent vision loss. Microperimetry offers a reliable method of visual field testing in patients with unstable or eccentric fixation due to macular disorders and provides correlation between retinal pathologies and functional defects. Self assessment with an Amsler grid frequently may fail to identify disease progression. The preferential hyperacuity perimeter is highly specific and sensitive in identifying new choroidal neovascularization.

MANAGEMENT STRATEGIES
The management of either type of AMD was a challenging task for the health care systems as well as the patients. The primary aim is to minimise visual loss and physical and emotional impairment and to optimise vision related quality of life. Increased comprehension and knowledge about basic pathological mechanisms in both type of AMD has led to novel developments in therapeutic strategies resulting in widening of available treatment and improved prognostic perspectives.

PROPHYLACTICTREATMENT (Prevention in intermediate and advanced AMD)
Although data in the literature are mixed with regard to each of age related eye disease study (AREDS) and AREDS...
Photodynamic therapy (PDT) with verteporfin (Visudyne) emerged as a welcome alternative to thermal laser because of its minimal collateral damage in the treatment of CNV. This technique employs intravenous administration of pharmacological photo sensitizer followed by physical activation of substance using a 689 nm laser light. The TAP22,23,24 and VIP25 studies provided evidence of the efficacy and safety of verteporfin therapy. This therapy reduces the risk of further loss in vision by 50%; however, an improvement in vision was still a rare event. Predominantly classic or purely occult lesions smaller than four disc diameters that showed recent progression were shown to have better outcomes. Considering the durability and need for fewer repeated treatments, in the pre-anti-VEGF era, PDT was an appropriate therapy for subfoveal CNV, new or recurrent, where the classic component is greater than 50% of the entire lesion ≤ 5400 μm2; or in an occult CNV when the visual acuity is worse than 20/50 or greater than 20/50 with a lesion size less than a disc diameter. The VIM trial 26 showed that PDT is beneficial in minimally classic CNV. ANCHOR trial27,28 demonstrated that PDT with verteporfin can retard the rate of visual loss, but does not confer gains in visual acuity when compared to anti-VEGF therapy. Combination therapy with IVTA and PDT helped only in prolonging the re-treatment interval. The benefit of ranibizumab with PDT as combination therapy remains unclear. DENALI study29 showed that ranibizumab and PDT (standard or reduced fluence) achieved inferiority to ranibizumab monotherapy as assessed by visual acuity. Combination therapy here lengthened the re-treatment interval. Combination therapy with ranibizumab and standard fluence PDT was found to be non-inferior to ranibizumab monotherapy with no difference in the proportion of patients with a treatment free interval of at least 3 months as evidenced in MONT BLANC study23,30. On the contrary EVEREST Trial31,32 showed that combination therapy is beneficial in polypoidal choroidal vasculopathy.

**ANTI VEGF THERAPIES**

Multiple studies have suggested that vascular endothelial growth factor increases vascular permeability and is involved in the pathogenesis of neovascularization in human eye disease. The current approach of Anti VEGF therapies are an important breakthrough in exudative AMD. The three Anti VEGF therapies currently approved by FDA for treatment of neovascular AMD are pegaptanib (macugen), ranibizumab (lucentis) and aflibercept (eylea). Pegaptanib an aptamer that specifically binds and inhibits VEGF isoforms containing at least 165 amino acids, was shown to delay the rate of vision loss in a large prospective randomised clinical trial. Visual acuity results are however limited. Ranibizumab an antigen binding fragment of a humanised monoclonal antibody directed against all the biologically active forms of VEGF-A, including the known active proteolytic breakdown products, effectively slows down the rate of visual loss and can improve vision as shown in prospective randomised clinical trial. Monthly injections provide superior sustained improvement in visual acuity and decreased central retinal thickness as compared with quarterly or as needed dosing. Overall intra vitreal ranibizumab is well tolerated and has a low rate of adverse ocular or systemic side effects. Bevacizumab is a full sized humanised monoclonal antibody with VEGF binding characteristics similar to ranibizumab; is approved by FDA for systemic treatment of metastatic colorectal cancer and lung cancer, but is an off-label treatment for neovascular AMD. A large prospective randomised clinical trial (CATT)33,34 showed that the visual outcome of bevacizumab was non inferior to ranibizumab. However the as needed therapy resulted in less visual gain than the monthly therapy of either drug. Bevacizumab was associated with a higher overall rate of systemic adverse events in the CATT trial, but most of the excess events have not been associated previously with systemic anti VEGF therapy. IVAN (randomised control trial of alternative treatments to inhibit VEGF in age related choroidal neo-vascularisation)35 trial at one year; the comparison by
drug was inconclusive. Bevacizumab was neither inferior nor equivalent to ranibizumab using the pre determined 3.5 non inferiority letter limit. As needed treatment was found to be equivalent to monthly treatment. Fewer patients receiving bevacizumab had an arterial thrombotic event or heart failure and there was no difference between drugs in the proportion having a serious systemic adverse event. Fewer patients in the monthly treatment group had fluid on OCT and dye leakage on fluorescein angiography at one year but no difference was found between drugs. Aflibercept is a recombinant chimeric VEGF receptor fusion protein that inhibits all VEGF isoforms and placental growth factors and inhibits VEGF-A with high affinity. The FDA approved dosing regimen – 3 monthly injections followed by injections every 2 months has been shown to have clinical equivalent effects as monthly ranibizumab in two large prospective randomised controlled trials. Future anti-VEGF therapies in the form of soluble fusion proteins, small interfering RNA's receptor tyrosine kinase inhibitors are being tried.

Since untreated neovascular age related macular degenera¬tion progresses to blindness and previously available treat¬ments did not achieve improvements on this scale ; anti-vascular endothelial growth factor therapy was hailed as the cure for neovascular age related macular degeneration. However there are drawbacks to anti-vascular endothelial growth factor treatment. Although initial worries that the eye might not tolerate repeated perforation or that serious adverse events (such as intraocular infection) might occur frequently have receded, the need for monthly monitoring and re-treatment, which creates a huge burden on resources, is a concern. There remains a theoretical possibility that long term inhibition of vascular endothelial growth factor could adversely affect the health of neural retina, the retinal pig¬mented epithelium, and choriocapillaris, since these tissues constitutively express vascular endothelial growth factor and rely on it for maintained health. 20% of people with neo-vascular age related macular degeneration treated with anti-vascular endothelial growth factor therapy have been shown to lose vision over time. A further proportion (about a fifth to a third) may lose the initial improvements in visual acuity, which may be the consequence of attempts to decrease the frequency of drug administration or may result from underlying disease progression. Another issue is the resistance to anti-angiogenic therapy which cannot be dismissed. Small case series suggest an increased rate of RPE tear after an injection though there is no study suggesting that this is higher than the rate in untreated patients after one year of evolution. Finally, the long-term systemic safety above 2 years has not yet been addressed. It is unlikely, however, that we will have better results in terms of safety concerns given the reduced life expectancy of patients with AMD and concomitant systemic disease (mean 7 years). These findings have dampened the initial enthusiasm for biological treatment to some extend.

**RADIATION THERAPY**

The rationale for radiation therapy was based on the known effects of radiation therapy on tumour microvasculature and its ability to prevent proliferation of vascular tissue by inhibiting neovascularization. The macular epiretinal Brachy therapy in age related macular degeneration (MERITAGE) showed that epimacular Brachy therapy (EMB) is safe and effective method for neovascular AMD. A phase 3 multicenter prospective randomized non inferiority desigined study called the CNV secondary to AMD treated with Beta Radiation Epiretinal Therapy (CABERNET) demonstrated an acceptable safety profile for epimacular brachy therapy at the two year mark and identified a subgroup of patients who tend to respond well to the treatment and required fewer rescue injections. However the CABERNET study did not achieve its primary end point with a 10% non inferiority margin and is not yet known whether we can identify these sub group of patients. Stereo tactic radio surgery (Iray system) which uses external beam radio therapy have also shown in its initial results at one year follow up in a phase 1 trial that majority of the patients showed improved or stabilized visual acuity with a mean visual acuity gain of 8-10 ETDRS letters. The INTREPID trial is on its way to evaluate the safety and effectiveness of stereotactic radio surgery in patients who have been previously treated with anti VEGF therapy thus epimacular brachy therapy and stereo tactic radio surgery may prove to be valuable adjuncts to anti VEGF therapy for neovascular AMD. Radiation therapy given in conjunction with anti VEGF agents may reduce the number of intra vitreal injections required. The risk of radiation related adverse effects appears to be minimal with these radiation treatments.

**STEM CELL THERAPY**

AMD, the commonest cause of irreversible visual loss in the developed world is characterized by loss of the RPE and degeneration of the overlying photoreceptors. Therefore, transplantation of healthy photoreceptors and/or RPE cells is an exciting option for future treatment of this disease. In the past, clinical studies employing this approach have involved autologous or allogeneic transplantation of retinal tissue. However, the former involves technical challenging surgery, while the latter involves use of fetal tissue, and thus both practical and ethical concerns. Moreover, both strategies have demonstrated only limited functional integration of transplanted tissue. In recent years, it has become clear that functional integration of transplanted retinal photoreceptors is possible, but is highly dependent on the differentiation stage of the cells in question. Since 1998, the advent of human embryonic stem cells offers the prospect of unlimited supplies of cells for transplantation, with tight control of
their differentiation state. Since 2007, the development of human-induced pluripotent stem cells raises the prospect of retinal transplantation with all the advantages of embryonic stem cell technologies, but without fears regarding immunological rejection, or ethical concerns. In 2012, preliminary results from the first human clinical trial of embryonic stem cells were reported in a single patient with AMD, with larger trials under way. Therefore, it is clear that stem cell based therapies are at the cutting edge of new therapeutic interventions for AMD, with many exciting breakthroughs likely in the coming years.

**Surgery for AMD**

Surgical removal of sub-foveal CNV, removal of sub-foveal hemorrhage, macular translocation, and transplantation of the pigment epithelium with or without choroidal graft are few of the surgical procedures evolved over the years in treating advanced AMD.

**Excision of CNV**

Removal of the CNV with submacular hemorrhage in AMD was first described by de Juan in 1988. The first visual results of membrane excision were disappointing with visual improvement in only 0% to 33% of the cases. The sub macular surgery trial (SSST) (1997 to 2003) evaluated removal of sub-foveal CNV compared with observation which showed that this surgical alternative therapy did not improve vision. A retrospective meta-analysis evaluating 647 cases of sub-retinal membrane excision in AMD subjects showed that improvement was achieved in about 33% and deterioration occurred in 27%. Recurrence rate of CNV was approximately 25%, and the progression of the atrophic scar size led to further visual loss. In a patient with recent macular hematoma secondary to CNV, different surgical options may be considered. The pneumatic displacement of the sub-macular hemorrhage with SF6 or C3F8, Vitrectomy, with TPA injection, hematoma removal, CNV excision, and gas tamponadhave been proposed with variable functional and anatomical results. Despite these limited results, there are still some indications for sub-macular surgery, such as for patients with low preoperative visual acuity due to large hemorrhagic or fibrotic membranes.

**Retinal Translocation**

Machemer in 1993 performed the first retinal translocation. The development of apical retinal rotation combined with a scleral shortening has been tested for several years. Because of the very small angle of rotation, the high rate of recurrence (approximately 50%), and the availability of other therapies (PDT), this technique is no longer implemented. A complete 360° retinotomy, which allows a higher rotation angle of the retina, has been proposed in the second eye-affected patients. Long-term reports have shown favorable visual results with 52% of the subjects having one or more lines of improvement, specifically reading vision and contrast sensitivity after one year. A high rate of PVR (approximately 30% of the cases in inexperienced hands and between 8% and 18% in experienced hands) limits the use of this surgical technique. However, retinal rotation with 360° retinotomy may be an alternative in very large CNV, when it does not respond to new therapies when it is associated with large hematomas.

**RPE Transplantation**

The disappointing visual results after CNV excision were explained by the simultaneous mechanical removal of the RPE layer and the transplantation of the RPE seemed to be a logical solution to restore vision. Currently, different techniques of autologous transplantation of the RPE are under evaluation. The iris pigment epithelial transplantation has been proposed, but this tissue is incapable of expressing crucial enzymes of the retinoid visual cycle. Investigators proposed the use of RPE suspension cells harvested through a nasal retinotomy at the beginning of the surgery and transplanted in the sub-retinal macular space after the excision of the CNV. A prospective trial was conducted with autologous suspension cell transplantation after membrane excision compared to membrane excision alone. At 12 months, visual improvement of two or more lines was achieved in 52.5% of the transplantation group (21.5% in the excision alone group), 32.5% remained the same, and 15% had a decrease of vision (21.5% in the excision alone group). The statistical analysis of far visual acuity showed just a trend in favor of the transplanted group, but the statistical analysis of the multifocal ERGs showed a significant difference between the two groups, with better results in the transplanted group. Another transplantation technique using a full thickness RPE-choroid sheet has been proposed by some researchers with interesting results regarding the long-term survival and the revascularization of the transplanted tissue. This technique uses an RPE-choroid flap taken in the superior mid-periphery, which is directly introduced through the macular retinotomy into the sub-retinal space. This particular technique, however, seems to be traumatic and presents a high rate of PVR.
again, we are faced with a new problem of repeated treatment.

unattainable results regarding improvements in vision. But newer pharmacologic interventions have led to previously and the role of VEGF in its development and persistence, we begin to better understand the pathophysiology of CNV.

The inability to improve vision in a majority of patients. As PDT appeared as a healthy alternative, but again, it was treatment benefit. Using non-thermal laser energy through angiogenic signals by facilitating or retarding endothelial angiogenesis, either by serving as angiogenic or anti-angiogenic signals by facilitating or retarding endothelial migration or tube formation, by de sensitizing vessels to regression through the process of vessel maturation, by inducing fibrosis, or by augmentation or diminishing VEGF or non-VEGF mediating signals. Thus potential treatment targets would be pigment epithelium derived factor, Notch family of receptors, platelet derived growth factor, transforming growth factor \( \beta \), Angiopoietin and Tie, matrix metalloproteinases, intergrins, angioatin and endostatin, and placental growth factor. Therefore, all the important VEGF is far from the entire story in angiogenesis. Thus the future anti angiogenic therapy would be targetting multiple pathways in combination with VEGF which will help in maximising treatment outcomes.

CONCLUSION

The last two decades, a multitude of clinical trials have evaluated the efficacy of various treatment modalities for neovascular AMD. Thermal laser successfully prevented the proliferation of CNV; however, visual loss and recurrences impaired the treatment benefit. Using non-thermal laser energy through PDT appeared as a healthy alternative, but again, it was unsatisfying to both the patient and treating clinician given the inability to improve vision in a majority of patients. As we begin to better understand the pathophysiology of CNV and the role of VEGF in its development and persistence, newer pharmacologic interventions have led to previously unattainable results regarding improvements in vision. But again, we are faced with a new problem of repeated treatment.

We are also now beginning to experiment with combination therapy in an attempt to discontinue the cycle of repetitive treatment. Although it appears promising, retrospective and small prospective studies are no substitute for large, randomized, controlled trials. As our understanding of the disease continues to grow at the molecular level, investigators are simultaneously exploring other treatment venues that may offer a more long-term solution, such as the inhibition of gene expression and signal transduction. So to conclude we are far ahead now in the treatment of AMD, but there is still a long way to go especially in prevention of this disease.

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