Abstract
Age-related macular degeneration (AMD) is the leading cause of blindness in elderly people in New Zealand and other developed countries. Neovascular AMD has a rapid onset and can lead to an overall loss of independence. Patients often present with an absolute central scotoma and distortion.

The pathophysiology of neovascular AMD is thought to be associated with polymorphisms and mutations in genes which are involved with the progression of the complement cascade. Vascular endothelial growth factor (VEGF) may contribute to the progression of AMD via excessive angiogenesis and permeability of vessels associated with the retina.

Current treatments for neovascular AMD act to reduce pathological angiogenesis via multiple mechanisms. Bevacizumab and ranibizumab bind to VEGF receptor 2 (VEGFR2), suppressing the actions of VEGF-A. Similar drugs, such as aflibercept, bind to placential growth factor (PIGF) in addition to VEGFR2, triggering similar effects. Endeavours to improve current treatments such as the safer use of broviluzumab and the use of the port delivery system for ranibizumab are being researched to maximise efficiency of therapies, to meet increasing demand.

There are many direct and indirect costs of AMD on patients and hospitals. With an ageing population who suffer from more comorbidities, AMD cases are expected to rise; we must therefore endeavour to improve existing treatments, and future techniques for management should not be discarded without serious consideration.

Introduction
Age-related macular degeneration (AMD) is the leading cause of blindness in elderly patients in developed communities. In New Zealand (NZ), AMD affects approximately one in seven people over the age of 50. This prevalence is similar to other developed countries: approximately 700,000 people suffer from neovascular AMD in the United Kingdom (UK), with the figure potentially reaching 1.3 million by 2050. In addition to the effects of sight loss, AMD costs the UK National Health Service (NHS) £1.3 billion GBP annually, largely due to the cost of treatments such as aflibercept. The progression of AMD leads to loss of central vision, leaving many patients unable to read, write, or recognise both colour and detail, thus compromising quality of life. Although the exact functional pathogenesis of AMD is not fully understood, there have been recent improvements in genetic technologies leading to the identification of various polymorphisms that have shown to harbour unique associations with AMD.

This essay will summarise some of the major components involved in the pathogenesis of AMD and the interactions between the major components, which lead to the development of the major pathological abnormalities. In this essay, “wet” or neovascular AMD will be focused on.

Classification and clinical manifestations
AMD can be classified into early and late phases. The early phase is characterised by the accumulation of lipid-rich subretinal deposits, called drusen. There are two clinical manifestations of advanced AMD: “wet” and “dry”. The cause of dry AMD is largely unknown but is thought to involve retinal cell death, which results in an inability to pick up light stimuli and convey information to the neurons leading to the primary visual cortex. It does not involve the leaking of blood vessels supplying the eye. Although there is no treatment for dry AMD, progress is much slower, often spanning over many months to years.

Neovascular or wet AMD has the most rapidly progressing vision loss compared to dry AMD. The scotoma is thought to be caused by damage to photoreceptors as a consequence of the growth of abnormal blood vessels in the sub-retinal pigment epithelium (sub-RPE) space. The growth of the new vessels is either from the retinal circulation, known as Type 3 macular neovascularisation (Type 3 MNV); or the choroidal circulation which pierces through Bruch’s membrane, known as Type 2 MNV. Both these mechanisms can result in changes in the anatomy of the choroid and retina; the exudations from these vessels can therefore lead to wet AMD. Fluid may accumulate in the retina, subretinal space, and sub-RPE. Patients tend to present with distortion, blurring, or a central scotoma, which is more rapid in onset in neovascular AMD. Patients with vision loss from late-stage AMD may also develop visual hallucinations. Hallucinations may be unformed (randomly coloured lights or patterns) or formed (involving actual objects, people, or scenes). As well as optical coherence tomography imaging, a thorough history is needed to diagnose neovascular AMD, as volunteers are unlikely to admit to these symptoms unless directly asked. In some cases, patients are barely aware of their symptoms, as they have developed strategies such as eccentric fixation to overcome their symptoms; Figure 1 exemplifies this process.

An overview of the pathophysiology and the past, current, and future treatments of neovascular age-related macular degeneration
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Eccentric Fixation:
1. Irreversible damage to photoreceptors in the macula.
2. Patients develop a central scotoma.
3. To compensate, patient develops a habit of focusing on a neighbouring location.
4. The initial target is projected onto a peripheral location.
5. The peripheral location = pseudofovea.

Pathophysiology
There have been a variety of proposed mechanisms which may lead to the development of neovascular AMD. Though the mechanism is uncertain, some studies suggest that the accumulation of oxidative stress, inflammatory cell infiltration, and genetic mutations, combined with environmental factors, lead to changes in the RPE and overall retinal anatomy. The underlying mechanism is thought to be a response caused by the complement cascade, which in turn alters the retina’s structure and action. This theory is reinforced by the presence of inflammatory factors in the drusen and the specific genetic variants related to complement factor proteins that consolidate the susceptibility to AMD. One of the most significant genes found was to be Complement Factor H (CFH).

As exemplified in Figure 2, CFH is a major inhibitor of the complement cascade at various levels. Firstly, it inhibits the conversion of complement component 3 (C3) to C3a/C3b, which are necessary for opsonisation during an inflammatory response. CFH also competes with Factor B to inhibit activation of C3b to C3bBb. (Note that C3bB = a C3bBb complex, which consists of C3 convertase binding to Factor B). Furthermore, CFH binds C-reactive protein (CRP), which reduces the inflammatory response via limiting CRP-mediated opsonisation. A genome association study investigating the ARMS2 locus found a single nucleotide polymorphism that was strongly associated with AMD in exon 9 of the CFH gene. This polymorphism changed tyrosine to histidine at codon 402, which is the position of the gene Y402H. This leads to a conformational change in the structure of CFH, leading to a decreased binding to CRP. This may cause overactivity of the inflammatory proteins.

A prospective study by Seddon et al. (2007) concluded that in the CFH gene, a single histidine allele C correlated with a 2.5 times increase in the risk of AMD onset; while a homozygous histidine variant genotype was correlated with a 6.35 times greater risk. This study was carried out in the United States of America (USA) between 1990 and 2001, with 1466 Caucasian participants. The mean follow-up time was recorded as 6.3 years and the AMD status was determined by grading fundus photographs. The study also carried out a predicted population-attributable risk (PAR) for the homozygous and heterozygous risk populations, showing they made up 20–60% of all AMD patients. The connection between AMD and the Y402H polymorphism was therefore established. This was a prospective study, meaning there is the possibility of bias in the results due to differential loss-to-follow-up.

Another study by Grassi and colleagues (2006) investigated the PAR of the Y402H risk variant for AMD among Hispanic and Asian populations, finding a PAR of 17% and 8% respectively. This brings into question the strength of the connection between Y402H and AMD. The study also showed that the environment and non-coding alleles may have had an impact on the development of neovascular AMD, which is beyond the scope of this article.

Vascular endothelial growth factor (VEGF) is also thought to have a role in the pathophysiology of neovascular AMD. The growth factor is spliced at various loci and so results in multiple different isoforms. VEGF-A 165 is crucial in the control of angiogenesis; in patients suffering from AMD, there are higher levels present. Many other isoforms are present physiologically, however for the purposes of neovascular AMD, VEGF-A is particularly important. Polymorphisms in VEGF encoding genes lead to an increased risk of AMD. The AMD risk allele C has been specifically identified as a unique polymorphism — it causes an increased risk of AMD in both homozygous and heterozygous populations. These polymorphisms lead to an increase in angiogenesis and vascular proliferation in pathological processes such as neovascular AMD.

The gene locus LOC387715/ARMS2 lies on chromosome 10q26; an insertion-deletion mutation here may also play a role in developing neovascular AMD. The mutant locus causes a significant increase in messenger RNA (mRNA) turnover by removing the polyadenylated tail, reducing the expression of the LOC387715 phenotype. The PAR for populations who were homozygous and heterozygous for the risk allele was 8.21 and 2.69 times greater risk respectively, relative to a no-risk population. By contrast, a different polymorphism leading to a mutant codon at the LOC387715 locus was shown to have a protective phenotype. To reiterate, in both cases, there is an instability in LOC387715. In the first (insertion-deletion) mutation, the risk is increased; but a premature nonsense mutation reduces the risk of AMD. This highlights the complexity of the genetic interactions that may have a hand in causing neovascular AMD. Many other genetic and non-genetic factors are involved; a few with particularly strong associations with neovascular AMD have been mentioned above.

Background of treatments
As established previously, neovascular AMD results from abnormal growth of blood vessels in the sub-RPE space. VEGF is vital for the growth of new blood vessels, particularly VEGF-A, which is involved in mitosis and regulation of endothelial cell survival and as a chemoattractant for endothelial progenitors from the bone marrow. Furthermore, VEGF-A is the most important inducer of permeability in the vasculature; it causes the formation of fenestrations between capillary endothelial cells by disrupting their intercellular junctions. VEGF-A’s functions are facilitated via the transmembrane receptor VEGFR2, which triggers a downstream cascade of signalling molecules such as kinases or protein phosphatases. The formation of perforations and vessels then allows the extravasation of inflammatory cells and fluid. Based on this, a pathological increase in vasculature (such as in neovascular AMD) results in an increase in oedema and an inflammatory response. This explanation is critical in understanding the basis of the management of neovascular AMD, the majority of which is car-
ried out via anti-angiogenic drugs. Previous therapy using pegaptanib sodium and verteporfin, as well as current therapies such as Avastin (bevacizumab) and Eylea (aflibercept) will be further explored below.

**Previous treatments**

**PEGAPTANIB SODIUM**

Pegaptanib sodium is an anti-angiogenic drug approved by the Food and Drug Administration (FDA) for wet AMD, but it is not recommended by National Institute for Health and Care Excellence (NICE) guidelines. Therefore, this treatment is no longer used to treat AMD. Pegaptanib sodium only inhibits isoforms of VEGF which contain at least 165 amino acids in its polypeptide; VEGF-A165 is a member of this group. It functions by binding to the 55 amino acid heparin-bind- ing domain of VEGF. These sites are not present in smaller isoforms of the VEGF family; as a result it does not affect the biologically active proteolytic products. The purpose of this selectivity is to reduce the abnormal angiogenesis present in neovascular AMD, whilst minimising inhibition of other smaller, physiological VEGF molecules.

**VERTEPORFIN PHOTODYNAMIC THERAPY**

Angio-occlusive therapy is a treatment that is no longer used to treat neovascular AMD, unless the patient has polypoidal choroidal vasculopathy. This therapy involves administering intravenous verteporfin, which is subsequently activated by a laser. Verteporfin accumulates in proliferating cells; in wet AMD, these are the endothelial cells of retinal microvasculature. The laser triggers a photochemical reaction which generates reactive oxygen species (ROS) in the endothelium. This causes platelet aggregation and thus the formation of a stable haemostatic plug, occluding the vessels selectively without affecting the overlying retina. However, altering the endothelium can lead to an increase in VEGF expression and cause angiogenesis, which is undesirable. This is one of the reasons for its discontinued use.

**Current treatments**

In recent years, treatments such as pegaptanib sodium have been replaced with newer treatments. Currently, treatments such as ranibizumab, Avastin (bevacizumab), and Eylea (aflibercept) are used as a first line of treatment for neovascular AMD. These drugs will now be discussed, as well as brolucizumab, which may be used to treat AMD but has recently been flagged for safety concerns by American Society of Retina Specialists (ASRS).

**RANIBIZUMAB AND AVASTIN**

Ranibizumab is a humanised antigen-binding fragment (FAB) of a monoclonal antibody, initially obtained from mice. It acts to selectively inhibit VEGF-A, including all its proteolytic products and isoforms. Ranibizumab prevents VEGF-A from interacting with VEGFR2 on the endothelial cell surface, limiting the formation of fenestrations, cell proliferation, angiogenesis, and leakage from vasculature. Ranibizumab prevents VEGF-A from interacting with VEGFR2 on the endothelial cell surface, limiting the formation of fenestrations, cell proliferation, angiogenesis, and leakage from vasculature.

Bevacizumab (sold under the brand name Avastin) is a common treatment for several conditions, including metastatic colorectal cancer, neovascular glaucoma, and neovascular AMD. Its mechanism of action is remarkably similar to that of ranibizumab; though both drugs are derived from the same parent molecule, ranibizumab is smaller and has been pharmacologically altered to bind more strongly to VEGF than bevacizumab. In New Zealand, Avastin is offered as the first-line treatment for neovascular AMD as it has fewer adverse side effects and is the considerably cheaper alternative to ranibizumab.

A case-series study conducted in 2007 reflects the success of Avastin in treating neovascular AMD. In the study, 79 eyes (from 74 patients) received an initial injection of bevacizumab to treat wet AMD. Among those who were followed up, mean central retinal thickness decreased from 304 +/- 83 micrometers at baseline to 237 +/- 105 micrometers at three months (p = 0.00002). There was also a mean improvement in visual acuity, from 20/100 at baseline to 20/80–1 at three months (p = 0.040). Twenty five percent of eyes from the patient in this study appeared to have a sustained response to a single injection and therefore did not require further injections. Though conducted retrospectively and with a small sample size, this study further supports the beneficial effects of bevacizumab.

**EYLEA**

Aflibercept, commonly sold under the brand name Eylea, is currently used as a second line treatment in neovascular AMD. Although it has been suggested that Eylea is more effective than drugs such as Avastin, Eylea costs significantly more than alternative treatments. According to the NICE technology appraisal 294, the total annual cost of treating an AMD patient is estimated at just less than £7000 GBP, which is based on a course of 8.5 injections; each vial of Eylea is priced at £816 GBP. Aflibercept is also indicated as a treatment in metastatic colorectal cancer and all stages of diabetic retinopathy.

Similar to the drug mechanisms described above, aflibercept binds and inhibits the action of VEGF-A and placental growth factor (PIGF), which is also a member of the VEGF family. There are two receptors that factors such as VEGF-A bind to: VEGFR1 and VEGFR2, respec-
Alongside new therapies, research is being conducted into a more convenient, safer way of administering existing treatments. A randomised controlled trial (RCT) on a port delivery system (PDS) with ranibizumab was conducted in 2019. It used a subconjunctival refillable reservoir of ranibizumab to release the antibodies in a controlled manner, eliminating the need for injections, which are invasive and expensive. This was a phase II trial, and although the results appeared promising, much progress needs to be made before this method of drug administration can be used in hospital settings.

Conclusion

Neovascular AMD is a severe, progressive condition, which can have many negative effects on a person’s quality of life. A person’s loss of visual function can have knock-on effects for their overall productivity and their ability to work and learn. In short, a person with neovascular AMD is at risk of suffering a loss of independence, as well as being burdened with related costs such as carers or nursing home care. The other direct costs of AMD on healthcare are excessive, and with an ageing NZ population who suffer from more comorbidities, the cases of AMD are expected to rise. Based on this, it is imperative that existing treatments for treating wet AMD are improved, and novel techniques for management are not discarded without serious consideration. As suggested above, there are many factors which influence the onset and progression of AMD; the more relevant pathways are currently targeted for much of the existing intervention. Although previous and current medications (such as those that block VEGF-A action) are efficacious, newer drugs such as brolucizumab and the use of a PDS are in early stages of development. Nonetheless, we can perhaps remain cautiously optimistic about the future of managing AMD.

References:


PORT DELIVERY SYSTEMS

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BROLUCIZUMAB

Brolucizumab, like other drugs mentioned above, works by inhibiting the action of VEGF-A. In 2019, the FDA approved the brolucizumab injection for the treatment of wet AMD; this was a result of two large-scale, phase III randomised controlled trials, called HAWK and HARRIER. The trials concluded that on average, brolucizumab had a larger correction in visual acuity at 48 weeks and caused a greater reduction in central subfield retinal thickness at 4, 8, 12, and 16 weeks, when compared against aflibercept.

Whilst it has been approved for use in several countries, including New Zealand, in February 2020, the ASRS reported severe side effects of Brolucizumab, such as retinal vasculitis, retinal haemorrhage, and cataracts, which can lead to vision loss. Though the drug is already in use, future developments would involve research into whether this drug could be made safer to avoid its potential adverse effects.

Future directions

Laser photocoagulation has been considered as a treatment for wet AMD since the turn of the century. This was done by using a laser to block newly emergent vessels at the expense of risk damage, such as to the retina, or accidental removal of normal vessels which thereby worsens the central scotoma. Although there are currently readily accessible anti-VEGF and anti-inflammatory therapies with a significantly higher efficacy and a dramatic reduction in iatrogenic risk, new treatments are being developed.

PIGF’s ability to bind and activate neuropilin 1 receptors, which is also to block newly emergent vessels at the expense of risking damage, thereby worsens the central scotoma. Although there are currently readily accessible anti-VEGF and anti-inflammatory therapies with a significantly higher efficacy and a dramatic reduction in iatrogenic risk, new treatments are being developed.


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