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REVIEW

Investigational drugs in clinical trials for macular degeneration

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ABSTRACT

Introduction: Intravitreal anti-vascular endothelial growth factor (VEGF) injections for exudative age-related macular degeneration (eAMD) are effective and safe but require frequent injections and have nonresponding patients. Geographic atrophy/dry AMD (gaAMD) remains an unmet medical need. New therapies are needed to address this leading cause of blindness in the increasing aged population.

Areas covered: This paper reviews the pathogenesis of macular degeneration, current and failed therapeutics, therapies undergoing clinical trials and a rationale for why certain AMD therapies may succeed or fail.

Expert Opinion: VEGF-inhibitors reduce both vascular leakage and neovascularization. Experimental therapies that only address neovascularization or leakage will unlikely supplant anti-VEGF therapies. The most promising future therapies for eAMD, are those that target, more potently inhibit and have a more sustained effect on the VEGF pathway such as KSI-301, RGX-314, CLS-AX, EYEP-1901, OTX-TKI. GaAMD is a phenotype of phagocytic retinal cell loss. Inhibiting phagocytic activity of retinal microglial/macrophages at the border of geographic atrophy and reducing complement derived activators of microglial/macrophage is the most promising strategy. Complement inhibitors (Pegcetacoplan and Avacincaptad pegol) will likely obtain FDA approval but will serve to pave the way for combined complement and direct phagocytic inhibitors such as AVD-104.

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Macular degeneration; geographic atrophy; wet AMD; complement; macrophage; microglia; clinical trials

1. Introduction

Macular degeneration is a chronic inflammatory disease of the retina with a strong hereditary component. In patients with the inherited AMD associated genetic polymorphisms the disease during the first five decades is asymptomatic and clinically undetectable. The earliest potential clinical biomarker of AMD, aside from the genetic polymorphisms, is abnormal dark adaptation which can precede clinically detectable drusen formation by up to 3 years [1]. The earliest clinically detectable sign of macular degeneration is drusen, (Figure 1(a)) (white yellow deposit seen predominantly in the macula) and/or retinal pigment epithelial changes, pigment clumping or autofluorescence disruption. (Figure 1(a, b)) [2] The character and number of drusen determine the early, intermediate, and late stage of initial dry macular degeneration but are not associated with vision impairment [3]. Vision impairment occurs during the late stage of AMD either the geographic atrophy (GA) or exudative form. It is difficult to predict which patients will develop GA, exudative, neither or both forms of advanced AMD making it difficult to perform preventative clinical trials.

GA is a localized sharply demarcated atrophy of outer retinal tissue, retinal pigment epithelium. and choriocapillaris that commonly starts extrafoveal and expands into the fovea [4]. (Figure 1(b)) GA can be seen as an absence of fluorescence in fundus autofluorescence and a exposed area on fundus photos (Figure 1(c)). Lesion location not size determines visual acuity, and as such, reduction in rate of lesion growth is the FDA approvable primary endpoint for GA trials. Vision impairment from center involving GA can be detected by visual acuity measurements, visual impairment from extrafoveal GA can be detected by microperimetry, reading speed measurements, and low light visual acuity, tests that are used as secondary end-points [5].

Exudative macular degeneration is the development of choroidal neovascularization in the macular region of the retina. These new blood vessels cause accumulation of subretinal, intraretinal, and sub-RPE fluid. Leakage can develop acutely and cause elevation of the retina and the symptom of metamorphopsia. If bleeding occurs, then a central scotoma develops. While considered a disease of neovascularization, visual acuity is mainly correlated to volume of leakage or bleeding rather than the size of choroidal neovascularization [6]. Clinically, volume measurements are performed with spectral domain high resolution optical coherence tomography (Figure 1(d, e) while CNV lesion size is measured with fluorescein angiography (FA) (Figure 1(f)) the decline in use of FA in the management of eAMD reflects the importance of fluid and blood volume as clinically more important than size of neovascularization [7]. From an FDA perspective, BCVA improvement and stabilization remains the primary endpoint for

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Article highlights

- The most promising future therapies for eAMD, are those that target, more potently inhibit and have a more sustained effect on the VEGF pathway such as KSI-301, RGX-314, CLS-AX, EYEP-1901, OTX-TKI.
- These novel therapies have theoretical advantages but must demonstrate non inferiority and equivalency in safety to current anti-VEGF therapies which will be difficult to demonstrate clinically.
- Most experimental and failed treatments for gaAMD inhibit the complement cascade or production of inflammatory activators but do not directly resolve microglial/macrophage inflammation.
- Because gaAMD is an unmet medical need complement inhibitory drugs like Pegcetacoplan and Avacincaptad pegol which slow GA growth rate modestly will likely receive FDA approval
- The most promising therapeutic for gaAMD, AVD-104, resolves both complement and microglial/macrophage inflammation.

exudative AMD trials of novel therapies. To obtain superiority, the novel therapeutic must improve BCVA, reduce fluid, bleeding, and maintain these reductions better than current treatments a high hurdle to jump.

2. Pathogenesis of AMD

The pre-clinically evident stage involves a dysregulation of the complement, oxidative and lipid pathway. This dysregulation leads to the accumulation of complement proteins, oxidative byproducts such as carboxy ethyl pyrrole (CEP)/ malondialdehyde (MDA), lipid and cellular damage byproducts that accumulate in the retinal space to form and initiate drusen and the early dry clinical stage of disease [8].

The clinical demonstration that high dose zinc was able to reduce development of eAMD in a large clinical trial (AREDS) supports the role of inflammation in the development of advanced stage macular degeneration [9]. Zinc increases TNF alpha, IL-8, and IL-6 production and reduces IL-10 in LPS challenged macrophages indicating that Zinc polarizes macrophages toward the M1,M2a phenotype and reduces the M2d VEGF producing phenotype [10]. Zinc treated patients over five years maintained a reduction in eAMD but no benefit for gaAMD prevention. This clinical trial points to macrophage/microglial polarization as a determinant of advanced AMD phenotype.

The advanced AMD stage is initiated by the accumulation of byproducts which are recognized by retinal microglia cells (resident retinal macrophages) as damage associated molecular patterns (DAMPs) [11]. This recognition activates microglial cells to become phagocytic and produce inflammatory cytokines that recruit peripheral blood monocytes [12]. Microglial cells and recruited monocytes polarize between the phagocytic M1 phenotype or the VEGF producing M2D phenotype. Zinc supplementation as explained above can direct polarization away from the M2d VEGF producing state and protects long term against the development of eAMD. This clinical data supports the concept that the predominant species determines if GA or exudation will result. If M1 species predominate than eyes develop GA.

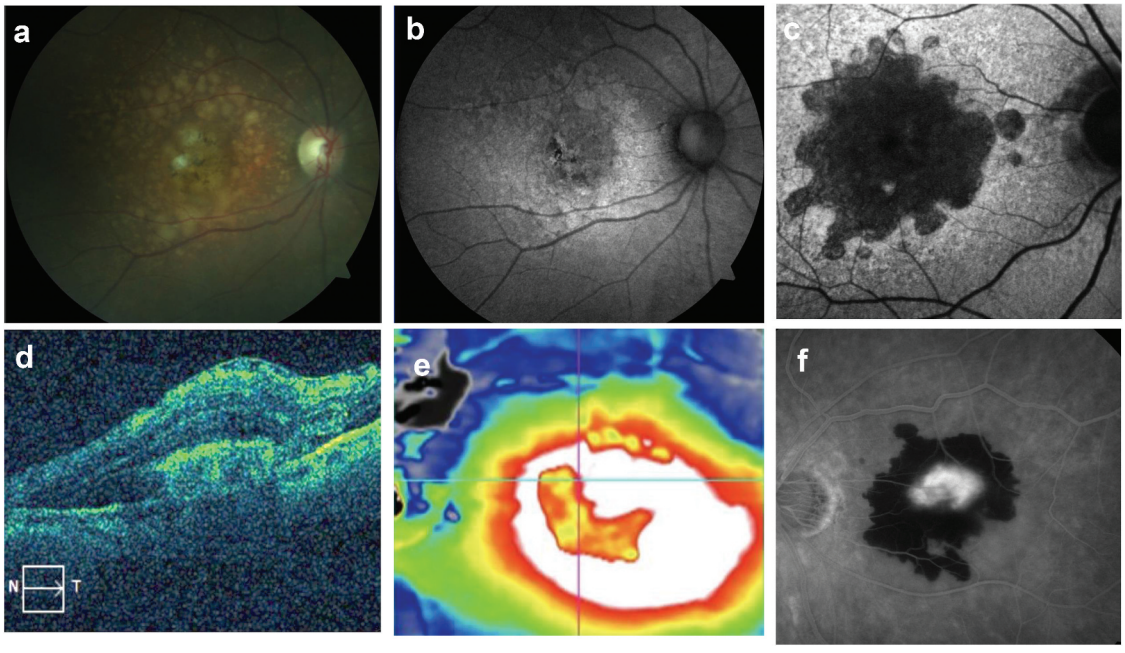

Figure 1. **Multimodal imaging of different stages of age-related macular degeneration**. (a) Color fundus photo of drusen stage dry macular degeneration of a patient whose best corrected visual acuity (BCVA) is 20/20. (b) Fundus autof luorescence (FAF) of same patient demonstrating the start of GA not visible on the fundus photo. (c) FAF of patient with extensive GA with a (BCVA) of 20/200. (d) Spectral domain optical coherence tomogram (SDOCT) cross sectional image of patient presenting with exudative AMD. (e) SDOCT topographic view of same patient where white represents elevation >400 UM and normal would be green (250 um). (f) Fluorescein angiogram of same patient showing central leakage and a ring of subretinal hemorrhage. This patient would not qualify for any clinical trial for exudative AMD.

If M1 polarizes to M2D then eyes develop exudative AMD. If both species are present than, eyes develop both GA and exudative AMD [8,13,14].

2.1. Pre-clinical AMD pathogenesis

The polymorphic genes that have been strongly associated with the development of macular degeneration can be stratified into complement, protease, and lipid regulatory genes. All these proteins lead to accumulation of byproducts in the retina which appear as drusen. For example, polymorphisms in complement factors H, 3 and B (CFH, C3, CFB) have been associated with progression from intermediate to large drusen and from large drusen to GA or CNV [15].

2.1.1. Complement pathway

Dysregulation of the complement cascade results in host cellular membrane damage, accumulation of complement factor proteins, cellular proteins, and membrane lipids [16].

The complement cascade is the non-cellular portion of the innate immune system or the immune systems first response system. The complement system consists of collection of serine proteases when activated results in the formation of a membrane attack complex that binds and lyses cellular membranes.

The complement cascade has three predominant activation pathways which converge on the formation of complement factor 3 (C3) convertase which represents the rate limiting step for the amplification and production of C5 and C5-9 the membrane attack complex. The complement pathway can be described in three stages, activation, amplification/inflammation, and lysis/resolution. The activating trigger defines the pathway. The classical and lectin activation pathways require the binding of antibodies or mannose respectively to activate the cascade. The alternative pathway, in contrast, is constitutively activated and is negatively regulated by CFH which prevents the amplification and lysis stages. The Alternative pathway is negatively regulated needs to be turned off with CFH, the Classical and Lectin Pathway need to be turned on [17]. (Figure 2)

2.1.2. Complement factor H (Alternative pathway)

CFH is a 155 KDa glycoprotein made up of 20 complement control proteins (CCPs) domains (short consensus repeat or sushi domains). The 1–4 CCP domains binds with variable affinity to C3b and factor I [18]. The C-terminal CCP domain 19–20 also binds to C3b via the C3d region. The 6–8 CCP domain of FH binds sialylated and asialic glycans found on Bruch's membrane, apoptotic, necrotic cells, DNA, MDA, C-reactive protein, and pentraxin-3 [19]. What this region binds determines the affinity of CFH to C3b. CFH when bound to a sialic acid glycans(self-associated molecular pattern (SAMP)) binds with higher affinity to C3 convertase (C3bBb) and displaces Bb degrading C3 convertase and preventing MAC formation [20,21]. When no appropriate sialic acid glycan binds to CFH then CFH/C3binding is weakened and C3 convertase can be formed resulting in the amplification of nonspecific lysis by MAC.

If CFH binds to a sialylated substances such as pentraxin-3, healthy Bruch's membrane, APO lipoprotein E, or LDL, CFH will bind with high affinity to c3b resulting in the degradation of C3 convertase. If bound to an asialylated molecule such as apoptotic cells, DNA, damaged necrotic cells, low sialic acid content LDL, and cleaved APO E proteins this will decrease CFH affinity to C3b resulting in amplification of C3 convertase, inflammation, and lysis [22]. (Figure 3(a) This regions ability to identify sialic acid as a SAMP make CFH a self-associated pattern recognition receptor that prevents the amplification/inflammation and

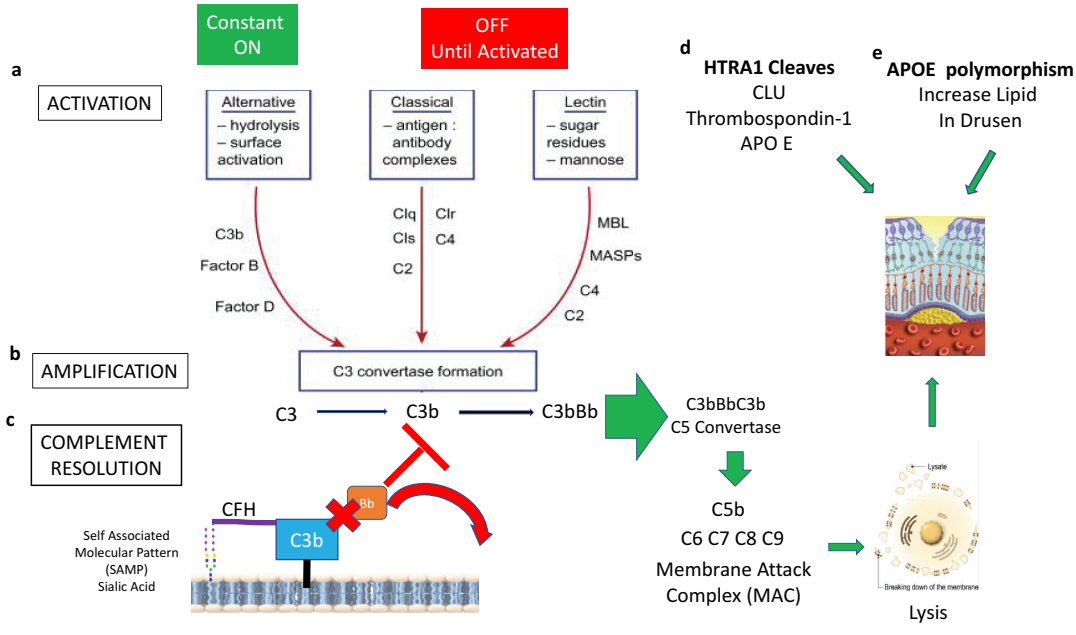

Figure 2. Polymorphisms in complement factors, HTRA1 and APOE lead to drusen formation and progression of AMD.

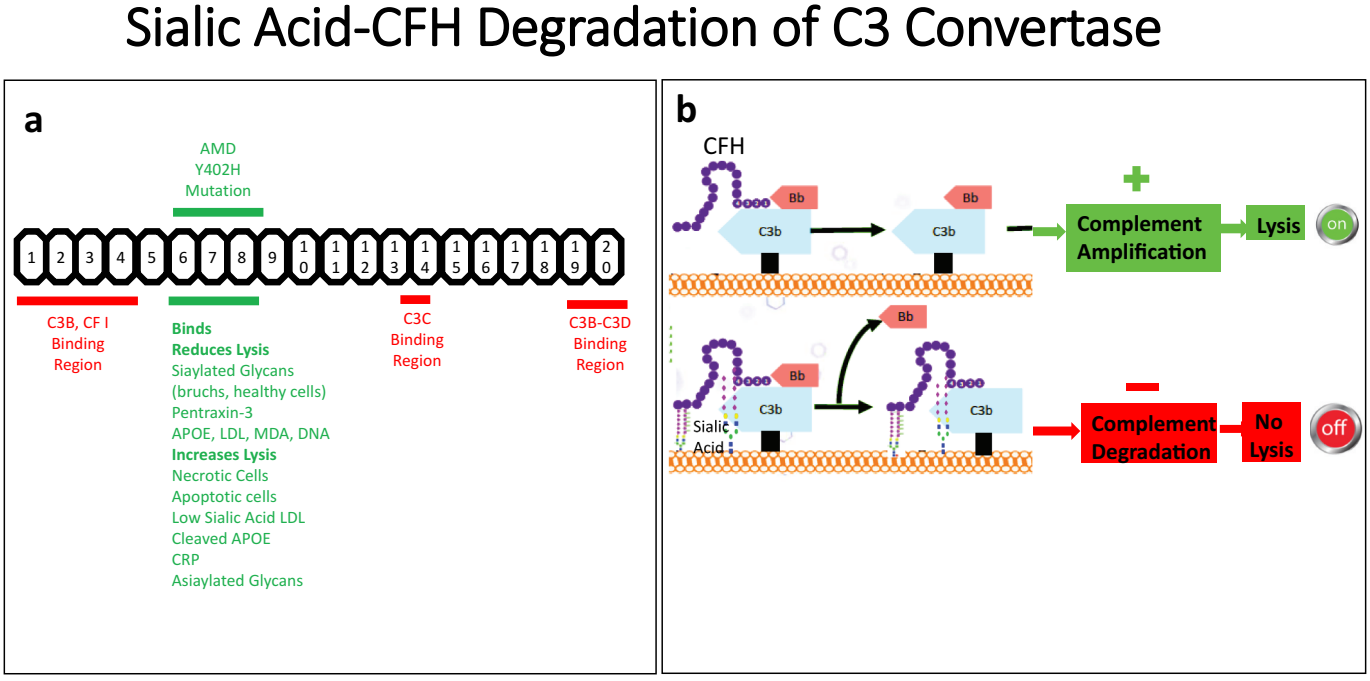

Figure 3. CFH Binding regions and Mechanism of Sialic Acid induced degradation of C3 convertase. (a) CFH Structure: CFH is a made of 20 CCPs the CCP 1–4 region is the C3b and CFI binding region. The CCP 6–8 region is the region where the Y 402 H polymorphism alters. This region binds sialylated molecules that activate CFH and reduce lysis. It also binds asialylated molecules that deactivates CFH and promotes lysis. CCP 13–14 binds C3C . CCP region 19–20 is C3B, C3D and sialic acid binding region. (b) Mechanism of CFH activation by Sialic Acid Ligands. CFH binds sialic acid this enhances C3b binding and displaces Bb resulting in the decay of C3bBb (C3 convertase). Without sialic acid then C3 convertase does not decay with resultant amplification of the complement pathway and membrane lysis with membrane attack complex.

lytic stage of the complement cascade from harming healthy host cells or substances such as APO E, LDL, or MDA. CFH meets the definition of checkpoint receptor that prevents autoimmunity. For CFH to work effectively a C3b-CFH-Sia complex is crucial for inhibiting complement amplification [23,24]. (Figure 3(b)

The Y402H polymorphism has the strongest association to AMD [25–29]. This polymorphism alters the CCP 6–8 glycan binding site on CFH and potentially reduces the efficacy of CFH to degrade C3 convertase resulting in chronic formation of MAC which damages and lyses host cells [30]. In AMD, drusen represent accumulation of expended complement factors evidence of chronic complement and innate immune activation. Evidence of complement activation is found in all stages of macular degeneration including the pre-clinical stage of AMD [31].

2.1.3. HTRA1/APOE polymorphism DAMP production

The ARMS A69S polymorphism increases the HTRA1 promotor activity. HTRA1 is a serine protease expressed in RPE cells and horizontal cells, and cleaves CLU an anti-inflammatory protein [32], thrombospondin-1 into a pro angiogenic fragment [33] and Apolipoprotein E a lipid metabolism proteins [34]. These cleavage products are found in drusen and represent DAMPs.

A polymorphism in Apolipoprotein E is associated with development of AMD. APO E binds to Complement factor H and polarizes macrophages to the M2 phenotype [35,36]. Dysfunction in APOE will result in hyperactivation of complement and the accumulation of lipids in microglial cells producing giant cells seen in histopathological specimens [37].

2.1.4. CEP and MDA activation of microglia and macrophages

The alternative pathway is also accelerated by the presence of a lipid oxidative byproduct of polyunsaturated fatty acids MDA. MDA modifies proteins in the posterior pole and is found in significant amounts in both drusen and lipofuscin an auto fluorescent substance often seen in advanced AMD. The eyes optical system intensifies photo-oxidative 400–500 nm high energy visible light onto the fovea. Due to the high lipid content and the high photo-oxidative stress on the macula, MDA is constantly being produced. To prevent constant inflammation in the retina, MDA is bound by FH at the CCP 7 region which prevents MDA modified proteins from inciting complement induced inflammation and macrophage uptake. The Y402H polymorphism reduces binding of MDA allowing this oxidative byproduct to initiate and propagate complement mediated inflammation [38].

CEP another oxidative byproduct of docosahexaenoic acid (DHA) also accumulates in drusen and AMD eyes [39,40]. In the retina, the photoreceptor outer segment contains large amounts of DHA and CEP [41]. While unprotected MDA modified proteins incite macrophage activation, CEP-protein adducts also activate macrophages to the M1 phenotype via the Toll Like Receptor 1 and 2 (TLR1/2) [42]. Microglia/

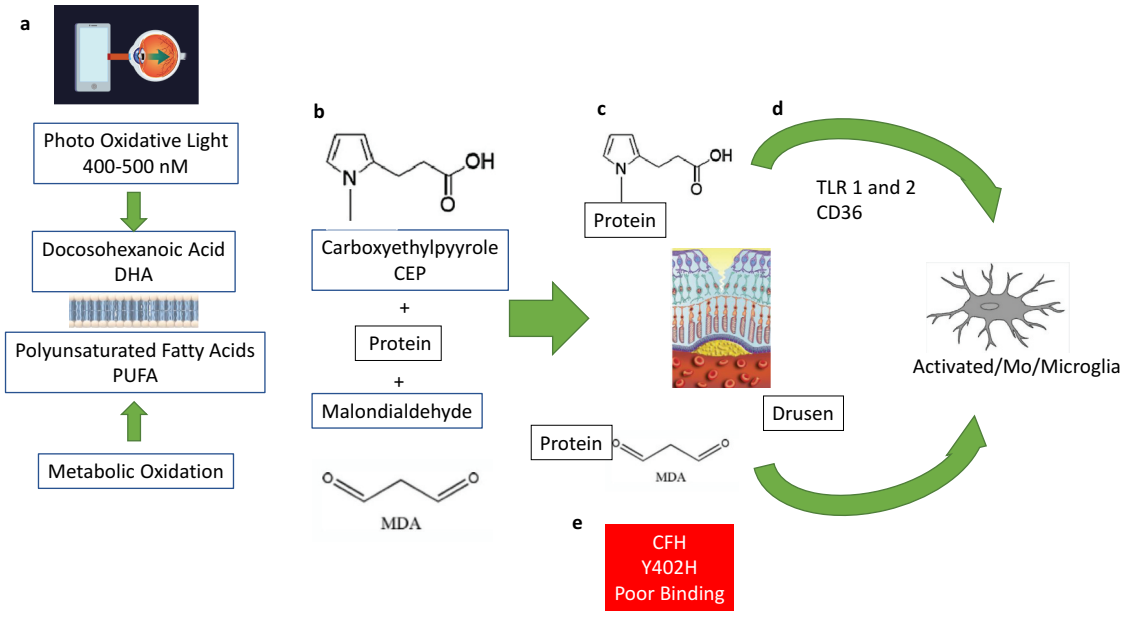

Figure 4. The role of photooxidative byproducts CEP and MDA in the activation of retinal microglial and peripheral macrophages. (a) Photooxidative light (400–500 nM) in addition to metabolic oxidative stress cause oxidation of fatty acids docoso hexanoic acid and polyunsaturated fatty acids producing. (b) Carboxyethyl pyyrole (CEP) and MDA respectively. (c) CEP and MDA modify proteins which are found in drusen. (d) CEP/MDA protein adducts bind TLR 1 & 2 and CD36 which activate microglia and macrophages. (e) MDA-protein adducts bind CFH at the CCP 6–8 which prevents complement activation. MDA does not bind CFH well with a Y402H mutation.

macrophages also scavenge and clear CEP via a CD36 and TLR2 mediated mechanism [43]. (Figure 4) AMD donor eyes contain M1 polarized macrophages versus non AMD donor eyes [44]. CEP-adducts can also induce an AMD phenotype in a mouse which point to the importance of macrophage activation in development of AMD [45].

In a C3 knock out mouse, high energy visible light exposure activated microglia, recruited macrophages and reduced the amoeboid phagocytic phenotype significantly in M1 macrophages [46]. This reduction in M1 polarized phagocytic macrophages, reduces phagocytosis indirectly and may explain how C3 inhibition can reduce GA. Macrophage/microglial polarization represent the end pathway for AMD and the switch that determines a GA or exudative AMD phenotype.

2.2. Early clinical stage AMD (drusen accumulation) pathogenesis

The dysregulation from genetic polymorphisms causes an accumulation of oxidative, protein and lipid initiating drusen formation and increasing drusen number, size, and volume. This DAMPs activate microglial cells. The microglia which represent the resident macrophages in the central nervous system is responsible for detecting and clearing oxidative byproducts, molecules released by damaged cells and misfolded proteins [47]. Activated microglial cells are phagocytic and can induce pyroptosis [48]. They also produce cytokines that recruit blood derived macrophages that surround drusen [37].

2.3. Advanced clinical stage AMD (GA/exudative) pathogenesis

The macula undergoes continuous light and metabolic oxidative stress and injury. The constant injury repair and resolution cycle is coordinated and counter-balanced by the innate immune and anti-oxidative mechanisms of the eye. The pathogenesis of AMD is the failure to modulate the injury-repair-resolution cycle [49].

In normal wound healing, the healing-resolution cycle has an activation phase followed by a fibrotic healing phase and an eventual resolution phase. This cycle is controlled by microglial/macrophage polarization state. When DAMPs are detected by pattern recognition receptors found on microglia and macrophages, macrophages and microglia are activated [13].

2.3.1. Role of microglia/macrophage polarization in advanced AMD

In AMD, unchecked complement activation from polymorphisms in the complement pathway produce an environment of constant microglial activation and macrophage recruitment. Microglia and macrophages in AMD are also triggered by lipofuscin accumulation, MDA adducts, CEP adducts, toll like receptor binding of DAMPs produced by lysed cellular membranes and asialylated intracellular proteins [50,51].

These activated microglia/macrophages cycle through several polarizations states, M1(phagocytosis, cytokine production) healing M2a,b,d (anti-inflammation, fibrosis, angiogenesis) resolution M2c(anti-inflammation, anti-fibrosis, anti-angiogenic) [52]. The conversion to the M2c phenotype requires sialic acid ligation of a sialic acid immunoglobulin like

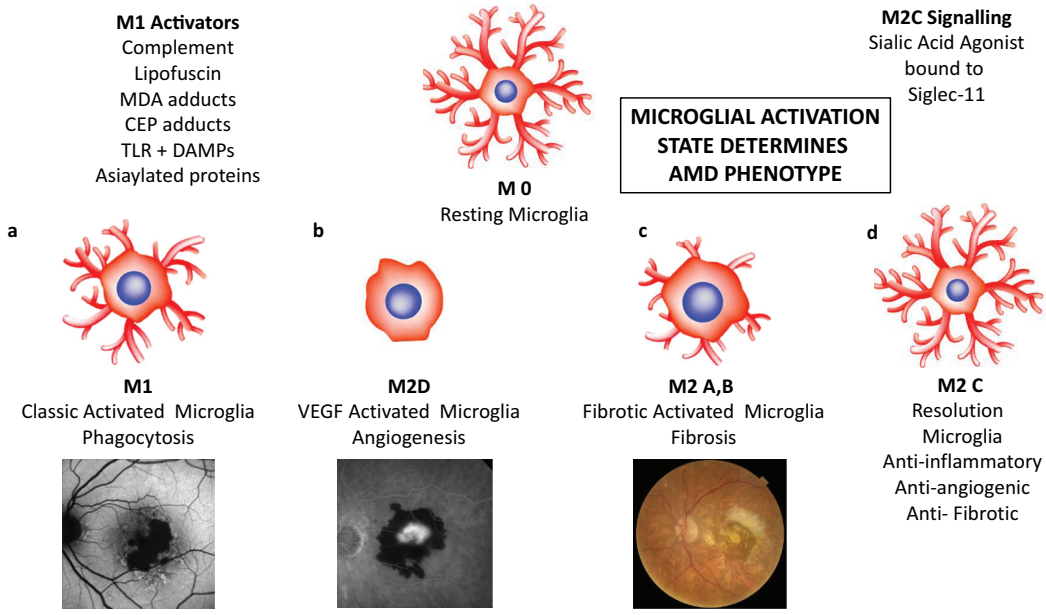

Figure 5. **Microglial/macrophage polarization state determines AMD phenotype**. (a) M1 microglia/macrophages are phagocytic and inflammatory which produces gaAMD. (b) M2 D microglia/macrophages are the VEGF producing pro-angiogenic macrophages that produces eAMD. (c) M2 A, B microglia/macrophages are fibrotic and produce disciform scarring. (d) M2 C microglia/macrophages is the resolution macrophage and can resolve both the gaAMD and eAMD.

lectin (Siglec) receptor, the proverbialSAMP receptors [53–55]. Sialic acid represents a signal to stop clearing and repairing since the microglia and macrophage have encountered sialylated healthy undamaged cells. Without this signaling, the inflammation, fibrosis, angiogenic phase would lead to chronic inflammation. Furthermore, a failure to transition can possibly halt the cycle at the inflammatory phase (M1, M2a) resulting in GA with chronic unchecked phagocytosis [56], or the proliferative phase (M2b, M2d) resulting in choroidal neovascularization and disciform scarring [57].

If the predominant macrophages/microglia species are polarized to the phagocytic M1 phenotype, then this could possibly increase the rate of GA, if the predominant macrophages are the M2D phenotype, the VEGF producing macrophage, then this possibly could lead to the exudative form. Life-long complement activation, oxidation and activated microglial production of sialidase [58] can result in the loss of the resolution signaling and subsequent retinal pathology (Figure 5).

2.3.2. Inflammatory microglia/macrophages (M1, M2a)

Inflammatory phase macrophages are the classically defined M1 phenotypes. These pro inflammatory M1,2A microglia/macrophage promote innate immune inflammation [59–63]. M1 macrophages have enhanced phagocytic abilities to facilitate removal of damaged, injured or senescent cells. Pro-inflammatory cytokines Il-6, TNF-alpha, Il-1b, and Il-12 are expressed and secreted by these inflammatory M1 macrophages [64,65].

The inflammatory phase M2a macrophage serves as the transition state to the proliferative phase. M2a releases anti-inflammatory cytokines IL-4 which inhibits M1 polarization of macrophages and promotes M2 polarization of macrophages. M2a macrophages also release arginase and Ym1 which promotes cell proliferation and migration. They also promote tissue formation by secreting IGF-1 [66–68]

2.3.3. Proliferative microglia/macrophages (M2b, M2d)

Proliferative macrophages M2b are responsible for glia and scar forming astrocyte induction, maturation of proliferating cells, stabilization of damage tissues, and angiogenesis [67–69]. These macrophages have a decrease in Il-12 and increase expression of Il-10, TGF-b, and Insulin like growth factor (IGF-1) [70].

The M2d macrophage is the VEGF producing macrophage and polarizes to this phenotype directly from M1 phenotype when M1 activation by Toll like receptors is accompanied by adenosine 2 A receptor activation by adenosine ligation [71]. The role of M2d is to revascularize wound and in oncology to promote tumor angiogenesis. In laser induced choroidal neovascularization, upregulation of lactic acid polarized macrophages to the VEGF producing phenotype while not upregulating VEGF in RPE cells or vascular endothelial cells [72]. In the laser induced CNV model, macrophages are necessary for the development of neovascularization [73]. These two studies implicate the VEGF producing macrophage in the development of CNV.

2.3.4. Resolution microglia/macrophages (M2c)

The resolution microglia/macrophage M2C is stimulated by the binding of appropriate sialic acid with Siglec [55]. Sialic acid, has been shown to resolve macrophage activation directly resolve phagocytic activity, vascular leakage, and inflammation [74]. In essence, sialic acid, exogenously presented as a SAMP was able to act as an anti-phagocytic and an anti-angiogenic at the same time. Sialic acid content of CSF diminishes with age [54,55]. This reduction in sialic acid reduces the resolution signal required by

activated microglia/macrophages to resolve inflammation [75]. Exogenously administered sialic acid mimetics could resolve chronic inflammation and treat the late stage of AMD [76].

The predominant therapeutic strategies being developed for GA/dry macular degeneration is to reduce activators of the microglial/macrophage inflammatory phase by blocking complement and reducing DAMP production. The predominant strategy for exudative AMD is to inhibit cytokines like VEGF and other angiogenic molecules. The limitation of these strategies is that reducing complement activity, DAMP formation or cytokine production reduces activators of microglia and macrophages but does not polarize these innate immune cells to the resolution state. Without a resolution signal, the macrophages will be fixed in the activation inflammatory or proliferative state. The reduction of activators is likely more beneficial for reducing drusen formation which involves complement activation, accumulation of damaged cells (membranes, proteins, DNA), cleaved proteins, lipid oxidation, and accumulation. The following review of current and investigational therapies will be performed in the context of the pathogenic mechanism of early and late AMD.

3. Current treatments EAMD

Anti-VEGF intravitreal injections are the current standard of care for eAMD. Several Pegaptanib sodium, ranibizumab, aflibercept, and brolucizumab have received FDA approval. Prior to anti-VEGF therapies verteporfin and laser photocoagulation were utilized but have been supplanted by anti-VEGF injections. Due perception by retina specialist of inferior efficacy, pegaptanib sodium the first approved anti-VEGF drug is not widely used. Ranibizumab compared to Aflibercept requires monthly injections to maintain vision resulting in aflibercept being more widely used every 2 month intervals [77].

Aflibercept given Q8 weeks compared to brolucizumab given Q 8–12 weeks demonstrated non inferiority in 2 pivotal phase III trials the Hawk and Harrier [78]. These trials lead to the FDA approval of brolucizumab. A rare occlusive retinal vasculitis was discovered to occur in patients during the post approval surveillance of brolucizumab and has placed brolucizumab on clinical hold [79]. in the phase III Hawk and Harrier Study, uveitis was noted in 16 patients who received brolucizumab while only 1 patient who received aflibercept was recorded as having uveitis. No retinal vasculitis was recorded in the Hawk and Harrier clinical trial in patients receiving either brolucizumab or aflibercept [80]. A post FDA approval study demonstrated brolucizumab associated IOI was treatable with anti-inflammatory treatment such as sub-tenons Kenalog [81]. While brolucizumab q12 week provided a treatment burden advantage, safety issues are hindering its current and future clinical use.

In addition to the FDA approved anti-VEGF drugs, Bevacizumab a drug approved for cancer, is being compounded and used off-label. While Bevacizumab was not clinically developed for intraocular use, it was purified for intraocular use and pre-clinically developed and demonstrated safety and efficacy in a non-human primate model [82,83]. Bevacizumab is calculated to represent 50% of the prescribed treatment for eAMD in the United States and likely much higher around the world due to its cost benefit [84].

Aside from its cost benefit, non-pivotal randomized multicenter clinical trials versus ranibizumab have been performed and found bevacizumab to be non-inferior to the FDA approved drugs [85–88]. While a similar study has not been done comparing aflibercept, brolucizumab with bevacizumab a meta-analysis determined only a slight efficacy benefit of aflibercept and ranibizumab above bevacizumab [89]. The presence of an efficacious, safe inexpensive drug raises the development bar for novel therapeutics very high.

4. Current/failed treatments dry AMD /GA

There are currently no approved drugs for GA. But several drugs have failed in clinical trials which represent potential lessons for future therapies.

4.1. Lampalizumab (Genentech/Roche, South San Francisco)

Lampalizumab is a complement factor D inhibitor that failed to reduce the rate of GA enlargement in 2 identical pivotal phase 3 trials the Chroma and Spectri. Lampalizumab failure can be explained by inadequate inhibition of and non-critical role of CFD [90].

The complement pathway is a complex interplay of serine proteases that requires activation, amplification and lysis. This pathway involves multiple enzymatic processes. The most critical process is the formation of c3 convertase C3bBb. The alternative pathway is regulated by complement factor H which binds to c3b in order to displace Bb and degrade c3 convertase. This critical step is the ideal target for complement pathway inhibition. Complement factor D is important in producing the Bb portion of C3 convertase. While critical and rate limiting, inhibiting mature factor D may not be enough to reduce factor D adequately. Factor D is produced as a proenzyme and requires cleavage of 6-amino acid peptide for maturation. This cleavage is under the control of mannose-binding lectin–associated serine protease-3 which is involved in the lectin complement pathway. To inhibit factor D effectively in the majority of patients, inhibition of both factor D and its proenzyme may be necessary. The other possibility is that Factor D may not play such a critical role in the alternative pathway as thought, and may be more critical for the lectin pathway [91].

The primary endpoint for GA trials is reduction in growth of GA size, measured by fundus autofluorescence. Loss of fluorescence represents cellular loss not retinal degeneration. Cellular loss result from pyroptosis and phagocytosis by macrophages and microglial cells. Retinal degeneration is initiated by complement damage which pyroptotically activate macrophages and microglial cells which stimulate the increase in atrophy [92].

4.2. Eculizumab (Alexion, Boston, MA)

Eculizumab is an IgG antibody inhibitor of complement component 5 (C5) and is FDA approved for atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria, both resulting from complement cascade dysregulation. The prospective, double-masked, randomized phase II COMPLETE trial evaluated intravenous eculizumab for reducing the growth of GA in AMD. While shown to be safe and well tolerated with no cases of CNV or endophthalmitis, the drug did not decrease the growth rate of GA [93].

Eculizumab is an IgG antibody when systemically delivered cannot cross the blood retinal barrier [82]. Complement activation occurs in the extravascular space where IgG does not access. Contrast this with an intravitreal C5 inhibitor which has shown biologic activity. It is important to have bioavailability for therapeutic efficacy.

4.3. Emixustat (Acucela, Seattle WA)

Emixustat hydrochloride is a small molecule orally administered RPE 65 inhibitors. RPE65 is a visual cycle isomer hydrolase. Emixustat mechanism is to reduce 11-cis and all-trans-retinal availability which will slow the visual cycle and reduce accumulation of bisretinoids such as lipofuscin. A phase 2B/3 clinical trial failed to reduce GA enlargement [94].

Emixustat effectively inhibits the visual cycle as evidenced by the 55% of patients who developed delayed dark adaptation. The failure of emixustat reflects the non-causative role of bisretinoid accumulation in the development of GA. Lipofuscin, the bisretinoid A2E seen in AMD, is found in the drusen stage as well as the late clinical stage of AMD. It likely stimulates the development of all stages of clinical AMD, but is not causative. Inhibition of its accumulation would have no effect on atrophy growth.

4.4. Fenretinide

Fenretinide is a synthetic derivative of vitamin A that binds to the serum retinol-binding protein, this reduces production of bisretinoid A2E (as demonstrated in the abca4 $^{-/-}$ mice) [95]. A phase II, placebo-controlled, proof of concept trial, studied the efficacy of oral Fenretinide in patients with GA due to AMD but no significant reduction in GA was seen compared to placebo [96]. The lack of efficacy of this visual cycle modulator, like emixustat, indicates that lipofuscin is not critical in GA growth.

4.5. Sirolimus

Sirolimus (rapamycin) is a mammalian target of rapamycin inhibitor developed and approved to prevent renal transplant rejection [97]. A randomized, controlled single-masked multicenter phase II trial of monthly intravitreal 440 ug sirolimus versus sham did not reduce rate of GA growth at 24 months [98]. Sirolimus modulates T-cell and Treg cells, the adaptive immune system, which make it effective in transplant rejection. GA is mainly mediated by phagocytic microglial/macrophage cells with minimal influence by T cells.

To effectively treat GA, the target must align with the clinical endpoint. VEGF was not discovered through genomic correlation, or inhibition of disease stimulating factors, it was targeted due to its effect on vascular permeability. The major cause of vision loss in exudative AMD remains intraretinal/subretinal fluid volume. Anti-VEGF medicines are not effective at reducing the lesion size or slowing retinal degeneration but are very effective at reducing retinal fluid and exudation [99].

To target GA growth rate a therapeutic must stop innate immune microglial/macrophage phagocytosis and clearing of cellular debris. As Sirolimus failure confirmed, the adaptive immune system does not likely have a direct influence on GA.

5. Drugs in clinical trials for EAMD (Table 1)

The drugs in development for eAMD can be categorized as novel anti-VEGF delivery, anti-VEGF, bispecific anti-VEGF, and non-anti-VEGF targets. Current anti-VEGF therapeutics have revolutionized the eAMD treatment. Frequent injections, non-responders, and inability to reduce CNV size, leaves some room for improved therapies. Novel delivery, molecules and targets are being pursued to develop investigational therapies for exudative AMD which will be reviewed.

5.1. Novel delivery of Anti-VEGF therapeutics

5.1.1. Port delivery system (Genentech, South San Francisco)

The port delivery system (PDS) is a surgically implanted reservoir drug delivery device designed to deliver ranibizumab [100]. The device seeks to reduce injections to twice a year.

Table 1. Current and investigational therapies for eAMD categorized by mode of action and trial phase.

Anti-VEGF	Bi-Specific Anti-VEGF	Gene therapy	Non-VEGF anti-angiogenic	Tyrosine kinase	Sustained delivery	Anti-Inflammatory
Current Treatments	**Finished Phase III**	**In Phase III**	**Entering Phase II**	**Finished Phase II**	**Finished Phase III**	**Finished Phase II**
Bevacizumab	Faricimab-RG7716	RGX-314	ICON-1	GB-102	Port Delivery Device	AKST4290
Ranibizumab	**In Phase II Trial**	**In Phase II**		PAN-90806	Ranibizumab	Xiflam
Aflibrecept	ATX-107	ADVM-022		**Finished Phase I**		
Pegaptanib Sodium	**Entering Phase II Trial**			CLS-AX		
Brolucizumab	IBI302			EYP-1901		
Finished Phase III				OTX-TKI		
KSI-301						
ONS-5010						
In Phase III						
Conbercept						
OPT-302						

The Phase II LADDER trial demonstrated that 79.8% of the 100 mg/ml filled PDS arm was not refilled at 6 months and maintained vision comparable to Q4 week ranibizumab. Initially 50% of patients developed vitreous hemorrhage which was reduced to 4.5% after surgical modifications [101]. The ARCHWAY Phase 3 multicenter, randomized, active comparator-controlled trial is evaluating patients with eAMD who receive the PDS with 100 mg/ml refills every 24 weeks versus monthly ranibizumab injections.

5.1.2. RGX-314 (Regen BioPharma, La Mesa, CA)

RGX-314 is a subretinal injected AAV8 vector delivering an anti-VEGF FAB fragment. A Phase I/IIa, open-labeled, nonrandomized, sequential assignment, dose escalation, multicentered trial of previously treated eAMD patients that required 4 anti-VEGF injections in the 8 months before trial entry [102]. This 5-armed dose escalation study had patients receive anti-VEGF injection of ranibizumab, if response they would receive RGX-314 3×10^9 genome copies (GC)/eye, 1×10^{10} GC/eye, 6×10^{10} GC/eye, 1.6×10^{11} GC/eye, and 2.5×10^{11} GC/eye, respectively. Rescue injection of ranibizumab, after anti-VEGF injection and RGX-314 was the main endpoint along with safety. The primary safety and tolerability of RGX-314 endpoint through 26 weeks in eAMD patient was met. The time to rescue in all cohorts ranged from 45.9 and 71.7 weeks since first anti-VEGF injection and no drug-related SAEs were observed [103].

5.1.3. ADVM-022(Adverum biotechnologies)

ADVM-022 is an intravitreally injected AAV.7m8 vector capsid that codes for aflibercept. A Phase I dose escalation, open label OPTIC trial evaluated 4 cohorts of patients testing 6×10^{11} and 2×10^{11}. The dosing cohorts were divided into patients taking 13-day course of oral steroids or 6-week course of steroid eye drops. The frequency of anterior and posterior chamber inflammation over time in the high dose was greater than the low dose cohort. Both doses reduced annualized injections by greater than 80% [104].

5.2. Anti-VEGF therapeutics

5.2.1. KSI-301(Kodiak Science, Palo Alto, CA)

KSI-301 is an intravitreally injected antibody phosphorylcholine biopolymer conjugate against VEGF. This drug remains at therapeutic levels for 4 months, has increased retinal penetration coupled with rapid systemic clearance as compared to current anti-VEGF drugs [105].

A Phase 1a single ascending dose escalation study in 9 patient demonstrated safety. Patients in the phase 1b open-label, randomized multicenter exploratory study in treatment naïve patients received either 2.5 mg or 5 mg of KSI-301. This study demonstrated good safety profile, and 55% of patients achieved a 6-month interval before mandated retreatment.

The DAZZLE phase 2, randomized, double-blinded, noninferiority multicentered, trials of KSI-301 in treatment-naïve eAMD patients. Cohort 1 receives 5 mg at 12-, 16-, and 20-week intervals after 3 monthly loading doses. Cohort 2 receives 2 mg of aflibercept monthly x 3 and then every 8 weeks. Mean change in BCVA from baseline at 52 weeks is the primary endpoint. After year 1, patients in the aflibercept treatment arm will be re-randomized 1:1 into KSI-301 5 mg and aflibercept 2 mg arms and re-analyzed at 96 weeks [106].

5.2.2. OPT-302 (Opthea limited, Victoria Australia)

OPT-301, a recombinant fusion protein that binds VEGF 3 receptor and selectively inhibits VEGF C/D. NCT03345082 a Phase 2b, randomized, double-masked, prospective, dose-ranging, multicentered, controlled study on intravitreal OPT-302 randomized patients in 1:1:1 ratio [107]. Group A received monthly 2 mg of OPT-302 along with 0.5 mg of ranibizumab. Group B received monthly 0.5 mg of the agent OPT-302 with 0.5 mg of ranibizumab. Group C received monthly 0.5 mg ranibizumab alone. Mean BCVA change at 24 weeks, Group A- 14.22 letters, Group B – 9.44 letters, Group C-10.84 letters [108]. Group A showed a superiority with a gain of 3.4 letters compared with Group C. Group A had more patients gaining 15 or more and less patients losing 15 or more ETDRS letters than Group C at 24 weeks serving as a secondary endpoint. The promising results of this Phase 2b study led to the current Phase 3 trial.

5.2.3. Conbercept (KH902, Chengdu Kanghong Pharmaceutical Group, Chengdu, China)

Conbercept (KH902), is a fusion protein with second Ig domain of VEGFR1 and the third and fourth Ig domain of VEGFR2 fused with Fc human IgG1. The structure is a bio-similar to aflibercept and has already completed a Phase III trial in China [109].

The phase 3, prospective, double-masked, multicentered, sham-controlled, PHOENIX trial of intravitreal Conbercept in Chinese patients with nAMD randomized patients 2:1 to Conbercept versus sham. The first arm received 0.5 mg Q 4 weeks x 3 months followed by a Q12 week interval. The second sham arm received sham injections Q4weeks x 3 months, then 0.5 mg Conbercept Q4 weeks x 3 months followed by 0.5 mg Q 12 weeks. The cohort on Conbercept gained 9.20 letter versus 2.02 letters in sham group at 3 months ($P < 0.001$). At the 12 months timepoint showed no statistical difference in the BCVA improvement between the 2 groups, with 9.98 BCVA letter improvement in the Conbercept arm versus 8.81 letters in sham arm. Following this trial, Conbercept was approved in China [109].

In the United States 2 phase 3, randomized, quadruple-blinded, multicentered, dose-ranging trial of intravitreal Conbercept in patients with eAMD, the PANDA-1,2 trials, are recruiting and randomizing patients 1:1:1 to 3 arms and receive 0.5 mg of Conbercept, 1.0 mg of Conbercept, or 2.0 mg aflibercept. All arms will receive monthly doses for the first 2 months, followed by doses every 2 months for the remainder of the 96-week trials. The primary endpoint is mean change from BCVA at 36 weeks [110].

5.2.4. ONS-5010/Bevacizumab-vikg (Outlook Therapeutics, Iselin NJ)

ONS-510 is a recombinant humanized monoclonal antibody (mab) that neutralizes all isoforms of VEGF. It is a biosimilar to

bevacizumab a drug currently being used off-label in patients with exudative AMD. The NORSE TWO phase III pivotal trial enrolled 228 eAMD patients, comparing ONS-5010 with Lucentis. The trial met both primary and secondary endpoints where 41.7% ($p = 0.0052$) ONS-5010 subjects gained ≥ 15 letters of vision 56.5% ($p = 0.0016$), ONS-5010 subjects gained ≥ 10 letters of vision 68.5% ($p = 0.0116$), ONS-5010 subjects gained ≥ 5 letters of vision ONS-5010 subjects gained 11.2 letters ($p = 0.0043$) in BCVA. There trial demonstrated an excellent safety profile [111]. There is a high likelihood that ONS-5010 will receive BLA approval.

5.3. Bispecific Anti-VEGF Therapeutics

5.3.1. Faricimab-RG7716 (Roche/Genentech, South San Francisco, CA)

Faricimab is a bispecific antibody with a modified FC region that blocks angiopoietin-2 and VEGF-A. A phase I study demonstrated visual and anatomic improvement in patients with treatment resistant neovascular AMD [112]. A Phase II multi-center, randomized, double-masked, active comparator-controlled trial (AVENUE) of intravitreal Faricimab versus ranibizumab showed that 1.5 mg Faricimab Q4 week arm had 9.1 letter gain at 36 weeks. This trial demonstrated efficacy and safety of Faricimab [113]. Another Phase II randomized double masked study (STAIRWAY) compared different injection intervals with q 4-week ranibizumab. The Q16 week Faricimab group gained 11.42 letters, Q12 week Faricimab group gained 10.08 letters and the Q4 week ranibizumab group gained 9.59 letters at the 52 week time point [114].

The results of 2 Phase III studies the LUCERNE and TENAYA randomized 1329 patients comparing Faricimab 6.0 mg up to every 16 weeks with Aflibercept 2 mg every 8 weeks. Faricimab was non-inferior to aflibercept in both studies with equivalent adverse events. These two pivotal trials have led to recent FDA approval of this drug for exudative AMD [115].

5.3.2. ATX-107 (Asclepix Therapeutics, Baltimore, MD)

AXT-107 is a synthetic 20-mer peptide, derived from non-collagenous sequences of the collagen IV protein. These proteins are involved in normal wound healing and downregulate angiogenesis at the later phases of wound healing. ATX107 has been shown to inhibit VEGFR2 and activate TIE2 [116]. The drug is delivered intravitreally and self assembles into a gel that sits in the inferior vitreous and delivers AXT-107 in a sustained manner.

A Phase I/II open-label, dose-escalating, 48-week study assessing the safety, tolerability, bioactivity, and duration of action of a single intravitreal injection of 0.1 mg, 0.25 mg, or 0.5 mg AXT107 has been enrolled but topline results have not been reported [117].

5.3.3. IBI302 (Innovent Biologics, Rockville MD)

IBI302 is a bispecific decoy fusion receptor protein that inhibits both VEGF and complement [118]. A Phase Ib 18 subject multi-intravitreal injection of IBI302 in patients with eAMD was well tolerated. The IBI302 group receiving 4 mg had an 8.0 letter improvement in BCVA and a mean central retinal thickness improvement of 134.3 um [119].

5.4. Tyrosine Kinase Inhibitors

5.4.1. GB-102 (GrayBug Vision, Redwood City, CA)

GB-102, an injectable bioerodable VEGF-A and platelet derived growth factor (PDGF) tyrosine kinase inhibitor. The Phase 1/2a, open-labeled, single-dose, multicentered ADAGIO trial of GB-102 in eAMD patients enrolled four dose escalating 8 patient cohorts receiving single dose 0.25, 0.5, 1, or 2 mg GB-102. Of the evaluable patients 88% at 3 months and 68% percent at 6 months were maintained on a single dose of GB-102 [120]. Decrease vision from microparticle dispersion in the anterior chamber occurred in the 2 mg cohort [102].

ALTISSIMO a Phase 2b, randomized, single-masked, multicentered, controlled study of GB-102 for CNV in neovascular AMD patients previously treated anti-VEGF injections were randomized to 3 arms. Cohort 1–1 mg of GB-102, cohort 2–2 mg of GB-102, and cohort 3 2 mg of aflibercept. The GB-102 arms received repeat injections every six months and the Aflibercept arm received injections every 2 months. After an interim analysis, GB-102 2 mg program was terminated. While the trial was not powered for non-inferiority versus aflibercept, the GB-102 1 mg trial arm ($n = 21$) had a 5-month median time to rescue therapy, and 48% of patients did not rescue for at least six months. Injection frequency was also reduced by 58% compared to patients' pre-trial anti-VEGF treatment regimen. Particle migration to the anterior chamber was seen in 4 of 51 injections and no surgery was required to evacuate the anterior chamber [121].

5.4.2. PAN-90806 (PanOptica, Mount Arlington, NJ)

PAN-90806 is a tyrosine kinase inhibitor of VEGF-A and PDGF in a topical eyedrop formulation. Previous phase 1/2 confirmed role as monotherapy in eAMD patients over 8 weeks of treatment and as a maintenance therapy in eAMD following singe injection of ranibizumab for 12 weeks. Punctate keratopathy due to off target inhibition of corneal epithelial epidermal growth factor receptor occurred.

A Phase 1/2, randomized, double-masked, uncontrolled, multicenter study in treatment naive eAMD patient (PAN-01-102 Trial) randomized patients 1:1:1 to receive 2, 6, or 10 mg/mL drops daily for 12 weeks. Patients were screened weekly and were allowed rescue injections 2 weeks after initiation of drops. Fifty one percent of patients did not need rescue at the week 16 visit and 88% of these patients not needing rescue showed clinical stability or improvement. No serious adverse events were noted by the safety monitoring committee [122]. Currently a Phase III program has not been announced.

5.4.3. CLS-AX (Clearside Biomedical, Alpharetta, GA)

CLS-AX is an injectable suspension for axitinib, a tyrosine kinase inhibitor currently approved to treat renal cell carcinoma. It directly inhibits VEGF receptors 1–3 and is formulated for delivery into the suprachoroidal space [123]. A Phase 1/2a open label single dose escalating study enrolled patients in successive 3 successive cohorts of 5

patients with previously treated eAMD. The procedure and the drug were well tolerated [124].

5.4.4. EYP-1901 (Eyepoint Pharmaceuticals, Watertown, MA)

EYP-1901 is a durasert implant that is delivering vorolanib, a tyrosine kinase inhibitor. A Phase I study on previously treated eAMD patients demonstrated 53% of patients did not need rescue at 6 months. While oral vorolanib caused systemic toxicity, the intravitreal implant was well tolerated. A Phase II is being planned [125].

5.4.5. OTX-TKI (Ocular Therapeutix, Bedford MA)

OTX-TKI is an intravitreal small molecule TKI (axitinib) eluting bioresorbable hydrogel implant that is undergoing a Phase I trial that has demonstrated durable response and a favorable safety profile [126]. The implant is targeting 6 months or longer delivery. A Phase I Open-label, dose-escalation study is underway in Australia. This trial has 4 cohorts that will be enrolled sequentially and will be dosed 200 ug, 400ug, 400ug + anti-VEGF and 600ug. Primary endpoint is time to rescue therapy and over 50% of subjects with eAMD did not need rescue therapy at 6 months. The drug was also tolerated and demonstrated no safety signals [127]. Further clinical trials will be performed.

5.5. Non-VEGF Therapeutics

5.5.1. ICON-1 (Iconic Therapeutics, South San Francisco, CA)

ICON-1 is a recombinant modified plasma coagulation factor VIIIa protein linked to the Fc portion of a human Ig1. It binds to tissue factor, which is overexpressed in choroidal neovasculature of AMD. There is potential for ICON-1 to be combined with existing anti-VEGF medication. A Phase 1, open-label, dose-escalation, nonrandomized, multicentered study on single intravitreal injection of ICON-1 in patients with CNV due to eAMD showed no dose limiting toxicity with 60 ug, 150 ug or 300 ug and some biologic activity [128].

A Phase 2 randomized, double-masked, multi-dose, six-month signal-seeking EMERGE study, randomized to receiving 0.5 mg ranibizumab and 0.3 mg of ICON-1, 0.5 mg of ranibizumab only, and 0.3 mg ICON-1 enrolled 88 patients with newly diagnosed CNV and followed for 6 months. ICON-1 monotherapy group had mild reduction in CRT and stable BCVA. CNV decreased by 40% in the combination arm, 14.6% in the ranibizumab only arm, and 17.2% in the ICON-1 only arm at 6 months. No SAEs related to the drug occurred [129].

Another Phase 2 randomized, open- label, parallel, multi-centered study enrolled patients receiving initially aflibercept followed by 0.6 mg intravitreal injection of ICON-1 or aflibercept. Primary outcome measure is mean change in CNV area from baseline at 9 months [130].

5.5.2. AKST4290 (Alkahest, San Carlos, CA)

AKST4290 is an oral inhibitor against CCR3 the natural receptor for eotaxin. CCR3 when ligated with eotaxin modulates inflammation, immune cell recruitment, and neovascularization. Two single arm, open-label phase 2a studies AKST4290-201 and 202. The 201 trial was 400 mg dose monotherapy in Naïve eAMD patients. The 202-trial included anti-VEGF nonresponders. The 201-study showed that 83% of patients had stable vision 6 weeks after baseline. Both trials demonstrated no safety issues [131].

5.5.3. Xiflam (Ocunexus/InflammX Therapeutics, San Diego, CA)

Xiflam is an oral small molecule connexin43 hemichannel blocker. Connexin 43 is involved in inflammasome activation and inhibition of Connexin 43 prevents assembly of NLRP3 a critical step in the inflammasome pathway. Connexin43 is upregulated in several retinal diseases including eAMD. Xiflam is un upstream inhibitor of the NLR3 inflammasome complex. While clinical trials have been proposed, no results have been presented at this time [132].

6. Drugs in clinical trials for dry AMD GA (Table 2)

6.1. Complement system modulators

6.1.1. APL-2/Pegcetacoplan (Appellis, Waltham, MA)

APL-2/Pegcetacoplan is an aptamer inhibitor of the complement factor 3 (C3). A phase II, multicenter, placebo-controlled,

Table 2. Failed and investigational therapies for gaAMD categorized by mode of action and phase of trial.

ComplementTherapeutic	DAMPInhibitor	Neuro-Protection	CellularTherapy	Anti-Inflammatory	MacrophageModulator
Failed	**Failed**	**Failed**	**Failed**	**Failed**	**Failed**
LampalizumabEculizumab	EmixustatFenretinide	Brimonidine-DDS	NA	Sirolimus	NA
Finished Phase III	**In Phase III**		**Finished Phase II**	**Entering Phase I Trials**	**Entering Phase I Trials**
Pegcetacoplan	ALK-001		Palucorcel	AVD-104	AVD-104
In Phase III	**In Phase II**		**In Phase 1 Trials**		
Avacincaptad PegolIONIS-FB-LRx	FHTR2163		OpRegenCPCB-RPE1		
NGM621	**Finished Phase I**				
GT005	Elamipretide				
HMR59					
GEM103					
Entering Phase I Trials					
AVD-104					

randomized FILLY trial randomized patients to sham, Pegcetacoplan monthly or every other month (EOM). GA growth rate reduction of 29% (p = 0.008) monthly and 20% (p = 0.067) EOM as compared to sham treated patients was demonstrated. No difference in BCVA was noted. In eyes treated monthly 20.9% developed exudation while 8.9% of the EOM treated group developed exudation. Furthermore, two patients in the monthly group and one subject in EOM group developed endophthalmitis [133,134]. Despite these adverse events, the FDA granted Pegcetacoplan fast-track designation. Two pivotal Phase III trials, DERBY and OAKS, are pending results.

6.1.2. Avacincaptad pegol (Iveric, New York, NY)

Avacincaptad pegol is an anti-C5 aptamer that directly inhibits membrane attack complex formation. A phase II/III randomized controlled dose ranging study GATHER1 trial was a 2-part study. Part 1 randomized patients to 1,2, mg Avacincaptad pegol and sham. Part 2 randomized patients to 2 mg, 4 mg of Avacincaptad pegol and sham. The 2 and 4 mg dosed patients achieved a 27.3% (p value = 0.0072) and 27.8% reduction (p value = 0.0051), respectively, in the mean rate of GA growth as compared with the sham group [135] CNV was reported in the fellow eyes of 10 participants (3.5%), in the study eye of 3 participants (2.7%) in the sham cohort, 1 participant (4%) in the Avacincaptad pegol 1 mg cohort, 6 participants (9%) in the 2 mg cohort and in 8 participants (9.6%) in the 4 mg cohort. No endophthalmitis occurred in any of the arms. A second confirmatory phase III trial is underway (GATHER2).

6.1.3. IONIS-FB-LRx (Ionis Pharmaceuticals, Carlsbad CA)

Ionis-FB-LRX is an anti-sense molecule targeting complement factor production in hepatocytes. A recent Phase I masked, placebo-controlled single and multiple ascending dose studies in 54 healthy volunteers demonstrated reduced plasma levels of 56% with 10 mg dose and 72% with 20 mg dose after 36 days of multiple subcutaneous administration. Reduction in factor B, Bb were also seen in day 43. No safety signals were identified. Currently a Phase 2 adaptive design, masked placebo controlled GOLDEN trial is enrolling to determine if GA area growth rate can be reduced [136].

6.1.4. ANX007(Annexon Biosciences, Brisbane CA)

ANX007 is an ant1-C1q fab antibody fragment. C1q is the initiating complement factor for the classical pathway. A phase II single dose randomized sham-controlled ARCHER trial is currently enrolling. Patients will be randomized to cohort of 5.0 mg of ANX007 monthly, or every other month compared with control of monthly or EOM sham.

6.1.5. NGM621(NGM Biopharmaceuticals, South San Francisco, CA)

NGM621 is a humanized IgG1 monoclonal antibody engineered to potently inhibits activity of complement C3. A Phase I single/multiple injection dose escalation trial tested single dose of 2,7.5,15 mg or 2 doses of 15 mg. No change in GA size and no CNV formation or endophthalmitis. A Phase II multicenter, randomized, double-masked, sham-controlled CATALINA trial has been enrolled.

6.1.6. GT005 (Gyroscope Therapeutics)

GT005 is a sub-retinally delivered AAV2 delivered CFI transgene. A Phase I/II open label, dose escalation FOCUS trial is enrolling. Interim analysis shows patients tolerated drug well with surgery related mild AEs predominating. Two subretinal delivery techniques are being evaluated one intravitreal and the other orbital [137].

6.1.7. HMR59 (Hemera Biosciences, Waltham, Ma)

HMR 59 is an intravitreal administered adeno associated viral vector delivering a transgene of CD59. CD59 is a glycoprotein that reduces MAC formation. AAVCAGsCD59 for both dry AMD and eAMD (NCT03144999 and NCT03585556, respectively). Interim results of HMR-1001 a phase I single intravitreal injection of HMR59 (n = 17) demonstrate the treatment to be well tolerated, with no dose-limiting toxicity. Four (23.5%) eyes developed mild inflammation that resolved with topical steroids or observation, and two of these four subjects also required topical medication to treat raised intraocular pressure [138].

6.1.8. GEM103(Gemini Therapeutics, Cambridge, MA)

Gem103 is an intravitreally administered recombinant human complement factor H. A Phase 2a dose escalation ReGAtta trial first enrolled patients to receive 3 monthly 250 ug doses of GEM103 followed by enrolling patients who receive 500 ug. Fifty-five of 62 patients enrolled had loss of function variants in their CFH gene. Reduction in complement markers was consistent in all genotypes and GEM103 was well tolerated. No endophthalmitis was noted in any of the patient's mild iritis was found observed in 3 patients and one case of CNV developed. Study was not powered for detection of GA progression. The trial is ongoing [138].

6.2. Noncomplement targets

6.2.1. Brimonidine DDS (Allergan, Irvine, CA)

Brimonidine drug delivery system (DDS) is a biodegradable implant that delivers in a sustain release brimonidine and alpha-2 agonist a drug used to treat glaucoma. Brimonidine is cytoprotective and serves as the rationale for use in GA. A phase II randomized, multicenter, double-masked, 24-month study comparing Brimonidine DDS 132 and 264 ug compared to sham did not show significant difference in GA lesion growth at the 24-month time point. Subgroup analysis demonstrated difference in growth rate for the first 3 months. And in patients that had GA>6 mm^2 at baseline. It is unclear if a Phase III trial will proceed.

6.2.2. FHTR2163 (Genentech/Roche)

FHTR2163 is a Fab directed against high temperature required protein A1 (HtrA1). A phase I open-label, single ascending dose escalation and multiple-dose expansion study injected doses of FHTR2163 ranging from 1 to 20 mg with a second stage of patients given 3 20 mg doses every 4 weeks. The cleaved ocular protein Dickkop-related protein 3 cleaved by

HtrA1 remained low in eyes treated with FHTR2163 which served as a pharmacodynamic marker for HtrA1 inhibition [139].

6.2.3. Elamipretide (Stealth Biotherapeutics)

Elamipretide is a cardiolipin-protective small tetrapeptide that targets and protects mitochondrial cristae and promotes oxidative phosphorylation [140]. A phase I open label trial tested subcutaneous Elamipretide in 2 cohort of patients. The first cohort are patients with intermediate AMD with high-risk drusen without GA and a cohort with non-central GA. The outcomes of low luminance visual acuity were assessed at week 24. Patients with non-central GA (n = 15) showed a mean increase in low-luminance visual acuity of 5.4 ± 7.9 letters and BCVA of 4.6 ± 5.1 letters. The patients with high-risk drusen (n = 19) also demonstrated improvements in low luminance and BCVA. Adverse events were mostly limited to reactions in the injection site [141]. A placebo-controlled phase II trial, ReCLAIM-2 is currently enrolling.

6.2.4. ALK-001 (Alkeus Pharmaceuticals, Cambridge, MA)

ALK-001 is vitamin A modified with a deuterium isotope replacement at carbon 20 (C20-D3-vitamin A), decrease the accumulation of toxic byproducts of the visual cycle in particular lipofuscin bisretinoid A2E [142]. A Phase III randomized, placebo-controlled SAGA study of oral ALK-001(C20-D3-vitamin A) in subjects with GA due to AMD has enrolled [143].

6.3. Cellular therapy

6.3.1. OpRegen (Lineage Cell Therapeutics)

OpRegen is a terminally differentiated retinal pigment epithelial cell line derived from pluripotent cells subretinally transplanted into patients with GA. A phase I/2 a study has enrolled 4 patients with dry macular degeneration and has improved visual acuity as compared to untreated eye for a period up to 15 months [144].

6.3.2. CNTO-2476 Palucorcel (Jansen Biotech,)

Palucorcel (CNTO-2476) is a human umbilical cord tissue derived cell compound. A phase I/II dose-escalation study injected subretinal CNTO-2476 into patients with GA. After 1 year, 34.5% (10/29) and 24.1% (7/29) experienced a ≥10 and ≥15-letter gain in BCVA, respectively. Most adverse events were related to the delivery procedure – 17.1% (6/35) of subjects experienced retinal detachments and 37.1% (13/35) experienced retinal perforation [145]. A multicenter, open label phase 2b study was performed in GA patients who received a subretinal injection of Palucorcel. No patients had retarded growth of GA significant improvement in BCVA [146]

6.3.3. CPCB-RPE1 Implant (Regenerative Patch Technologies, Menlo Park, CA)

California Project to Cure Blindness Retinal Pigment Epithelium (CPCB-RPE1) implant is RPE cells derived from embryonic stem cells which are placed as a single layer on a thin membrane has undergone a Phase 1/2 clinical trial which demonstrated some initial adverse events in the first cohort which was mitigated in the second cohort. The study was insufficiently powered to demonstrated clinical efficacy [147].

6.4. Macrophage/Microglial Modulator

6.4.1. AVD 104 (Aviceda Therapeutics, Cambridge MA)

AVD-104 is a sialic acid mimetic nanoparticle that binds to Siglecs and CFH that polarizes microglial cells and macrophages to the M2 resolution state and increase binding of CFH to C3b promoting the degradation of C3 convertase and inhibition of the complement pathway. A Phase 1/2 adaptive design is planned but not currently enrolling.

7. Conclusion

Current anti-VEGF therapies for exudative AMD have set a high bar for investigational therapies. Investigational therapies for exudative AMD are focused on reducing frequency of injections, inhibiting other angiogenic factors and inflammation. Clinically, intravitreal injections are efficacious, safe, tolerable, and convenient, so these investigational drugs must meet a high standard for safety and convenience. Developing a superior drug to current therapies would be difficult and only a few drugs are attempting to demonstrate superiority.

GA remains an unmet medical need. Unlike the development of exudative AMD where the main effector of pathology, VEGF, is inhibited, much of the focus is on stopping the pathway leading to, rather than stopping phagocytosis. Because the FDA approvable endpoint for GA is reduction in rate of lesion growth, reducing stimulators of phagocytic monocytes maybe approvable but will provide minimal benefit to patients. Directly stopping the phagocytotic microglia/macrophages will prove the best strategy.

8. Expert opinions

8.1. Exudative AMD therapies

The predominant role of VEGF in producing the blinding complications of eAMD identified VEGF as an ideal inhibitory target. This discovery was not deduced from genetic or biologic data, but rather clinical understanding of the true cause of vision loss or blindness from eAMD. eAMD is a neovascular disease, yet neovascularization alone does not cause visual loss. Vascular leakage, bleeding and scarring that are associated with neovascularization results in accumulation of macular fluid, blood and fibrosis with subsequent visual loss.

VEGF has been identified as the long-postulated factor x, a soluble angiogenic factor that causes vascular permeability and produces the blinding complication of eAMD. Even now the VEGF pathway remains the only inhibitory target that reduces both neovascularization and vascular permeability and only anti-VEGF medicines have remained the de facto standard of care supplanting laser and photodynamic therapy.

Anti-VEGF treatments currently are very effective and safe and set a high bar for the development of new therapies. Many investigational therapies such as Conbercept and ONS-5010 are biosimilar to current therapies and will likely gain approval. Market forces will determine their clinical utilization.

Investigational treatments that inhibit the VEGF pathway either as a TKI, gene therapy or novel polymer inhibitor seek to reduce treatment burden, but the risk of these strategies lie in the potential toxicity of some of these novel molecular entities and delivery devices.

Examples of potential safety signals are found in the PDS, ADVM-022, and GB-102. The PDS has received approval for use by the FDA but risk of surgical complications during implantation remains a concern. ADVM-022 requires steroid pretreatment to attenuate inflammatory response seen in viral vector treated patients. GB-102 also has reported idiosyncratic safety issues that may prevent its eventual approval.

KSI-301 does show differentiation and appears to last longer than current anti-VEGF drugs and theoretically has similar and acceptable safety characteristics. If KSI-301 demonstrates equal efficacy with longer injection interval than it has the potential to be the dominant anti-VEGF therapy. Other sustained release TKI inhibitors CLS-AX, EYEP-1901, OTX-TKI also hold promise but there is still a theoretical safety concern.

Anti-VEGF plus therapies such as OPT-302, Faricimab, AXT-107, IBI302, and ICON-1 focus on more potently inhibiting other stimulators of neovascularization. While lesion size is associated with some improvement in BCVA [148,149], other factors such as leakage and bleeding are not addressed by these type of therapies. Faricimab demonstrated noninferiority to aflibercept with potentially less frequent injections. It is unclear if this improvement in duration is due to the higher dosage or the inhibition of angiopoietin-2. OPT −302 is the most promising of these anti-VEGF plus drugs since it blocks VEGF C/D which will provide complete inhibition of the whole VEGF family.

Anti-inflammatory therapeutics like AKST4290 and Xiflam, are general anti-inflammatories that may reduce the production of VEGF but will not be additive to anti-VEGF effect in regards to vascular permeability or neovascularization.

The most promising next generation exudative AMD treatments are KSI-301, RGX-314, CLS-AX, EYEP-1901, OTX-TKI. These treatments theoretically balance prolonged intravitreal drug. Concentration, with safety and efficacy. Pivotal clinical trials will determine if these therapeutics fulfill their promise.

There remains a subset of non-responding anti-VEGF treated patients that have persistent leakage and lesion growth despite aggressive anti-VEGF therapy. These patients are the unmet medical need in eAMD. To develop therapies for this subset of patients other vascular permeability factors involved in eAMD must be elucidated and inhibited. These other vascular permeability factors are likely produced by inflammatory mediators since AMD is a disease of chronic innate immune activation. While VEGF is a cause of inflammatory vascular leakage, other factors are likely involved in these patients who have inadequate response to anti-VEGF therapy. This is demonstrated clinically by the effectiveness of steroids to reduce inflammatory swelling where VEGF is not involved. Our further understanding of cytokine stimulators of vascular permeability must be progressed if we are to have an effective treatment for the anti-VEGF eAMD nonresponding patients.

8.2. GA therapies

In GA, visual impairment is caused by the loss of outer retinal cells. The main cells implicated in this loss are microglia and macrophages that are of the phagocytic morphology, in particular IBA-1 + microglia/macrophages which are found throughout the outer retinal area adjacent to atrophic areas in eyes with gaAMD. These IBA-1 + microglial cells are also in a hyper-ramified or amoeboid morphology which represent activated phagocytic microglia [150]. Furthermore electron microscopy studies have shown microglial cells loaded with lipid, or retinal substances in the outer retina in GA specimens [151]. These histological studies represent the smoking gun for phagocytic microglia and macrophages as the main effector for cellular loss in GA.

Because complement is genetically implicated in the development of drusen, eAMD and gaAMD researchers and drug developers have focused predominantly on complement inhibition. Logically complement inhibition would be preventative strategy akin to lowering cholesterol for heart disease or reducing blood pressure to reduce risk of stroke. But once a heart attack or stroke has occurred, lowering cholesterol or reducing blood pressure would not prove to be an effective treatment for the complication of heart attack and stroke.

Immunohistochemical analysis of GA specimens show complement deposition, in particular c5-9, is found mostly in the inner retina away from the atrophy of the outer retina. The lack of complement byproducts apposition to GA further support its indirect role in the progression GA.

While complement represents an indirect stimulator of GA growth, inhibiting complement can potentially attenuate GA growth by reducing stimulators of microglial/macrophage activation. The subtle delayed reduction in GA growth rate seen in late-stage clinical trials for complement inhibitors provides evidence of the indirect role of complement in gaAMD. For an unmet medical need, complement inhibitors such as Pegcetacoplan and Avacincaptad pegol will likely obtain FDA approval, despite the modest reduction in GA growth.

Lessons from the VEGF story can be applied to developing effective therapeutic strategies for gaAMD. The discovery of VEGF as the critical target was not discerned from genetic associations but by identifying and inhibiting the direct cause of neovascularization and vascular permeability. Using a similar approach, the end effector of vision loss in gaAMD is the phagocytic elimination of outer retinal cells mediated by microglial cells and recruited macrophages.

Unlike the complement cascade, microglia and macrophage polarization biology has only been elucidated in the last decade. This polarization biology is the answer to how one disease can lead to two opposing phenotypes (eAMD and gaAMD). While the M1 polarization state has been recognized as the phagocytic, inflammatory cytokine producing species only recently has the M2d VEGF secreting polarization state been identified and described. The discovery of M2d leads to the conclusion that predominant polarization species determines the development of eAMD or gaAMD.

Clinically we see supporting evidence of this conclusion with the 20.9% dry to wet conversion in the phase II clinical trial of Pegcetacoplan a C3 inhibitor. By reducing complement activators of microglia/macrophages, you reduce the M1 activation rate. In the presence of adenosine and the absence of a sialic acid resolution signal, the existing M1 macrophages will polarize to the M2d VEGF producing state initiating eAMD.

Understanding the determinants of microglial/macrophage polarization will prove to be the best chance for developing an effective safe treatment against gaAMD. Ligating the Siglec family of self-associated pattern recognition receptors will lead to profound attenuation of phagocytic pathology and GA growth.

AVD-104 is the first experimental therapeutic that can polarize microglia/macrophage to the resolution state [74,152,153]. In addition, AVD-104 can activate CFH to bind c3 with higher affinity resulting in degradation of C3 convertase [154]. Its ability to resolve macrophage activation and attenuate the complement cascade with one molecule make it the most promising of all the current investigational therapies for gaAMD. Defining and designing glycan modulators of microglial/macrophage polarization like AVD-104 will lead to a highly effective clinical therapy over the next several years.

Complement inhibitor development mimics the development pathway of the selective VEGF 165 inhibitor called pegaptanib sodium the first drug approved but no longer widely used. for eAMD. While effective, anti-VEGF therapies reached their potential once all the the VEGF-A isoforms were targeted (Ranibizumab, bevacizumab, aflibercept). Both the complement and microglial/macrophage activation branches of the innate immune system must be inhibited to realize the goal of a truly effective therapeutic for gaAMD.

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