

# Complement Factor 5 Inhibition in Age-related Macular Degeneration

ARC1905 shows promise for enhanced efficacy in eyes with wet AMD.

BY JORDI MONÉS, MD

**A**ge-related macular degeneration (AMD) is the leading cause of severe vision loss in the developed world. Although its exact pathogenesis has yet to be elucidated, AMD clearly has been shown to result from a chronic, aberrant inflammatory response, specifically involving the complement system.<sup>1</sup> In 2005, using DNA sequence data from the Human Genome Project, three independent groups demonstrated that a polymorphism (Tyr402His) in the complement factor H (CFH) gene increases the risk of developing AMD in whites.<sup>2-4</sup> Several other articles since the publication of these landmark studies have demonstrated the involvement of the complement system in the pathogenesis of AMD.<sup>5</sup> These studies have led to the hypothesis that localized disruption of the complement cascade may result in arresting the progression of AMD.

## THE COMPLEMENT CASCADE AND ITS ROLE IN OCULAR DISEASE

Over the past decade pivotal genetic, laser-induced CNV and human histopathologic and inflammatory biomarker studies have strongly implicated complement-mediated inflammation in the pathogenesis of both dry and wet AMD. The complement system is a biochemical cascade that helps or “complements” the ability of antibodies to destroy pathogens. As part of the innate (or nonadaptable) immune system, the complement system promotes inflammation, eliminates pathogens, and helps enhance an individual's immune response. The comple-

ment system consists of a group of more than 20 proteins generally synthesized by the liver, which circulate as inactive precursors, or pro-proteins. When stimulated by one of several triggers, proteases in the complement system can cleave specific proteins, in turn resulting in the release of specific cytokines and consequent initiation of an amplifying cascade of further cleavages, resulting in activation of the cell-killing membrane attack complex (MAC), which creates perforations within cellular membranes.

Three distinct biochemical pathways activate the complement system: the classical pathway, the alternative pathway, and the mannose-binding lectin pathway. The classical complement pathway is triggered by antigen-antibody complexes. The alternative and mannose-binding lectin pathways can be activated without the presence of antibodies (nonspecific immune response). Although each pathway is triggered differently, the common goal of these pathways is to deposit clusters of C3b on target pathogens. C3-convertase cleaves C3, creating C3a and C3b. C3b then binds to the pathogen surface, leading to internalization by macrophages and other phagocytic cells. C5a is an important chemotactic protein, helping recruit inflammatory cells. Both C3a and C5a have anaphylatoxin activity, leading to mast cell degranulation and increased vascular permeability. C5b also starts the membrane attack pathway, which leads to the formation of the end product of the complement cascade: the MAC. The MAC, consisting of

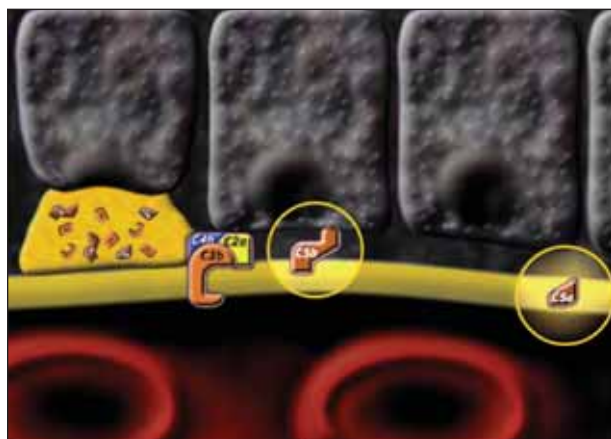


Figure 1. C5 cleaves into C5a and C5b.

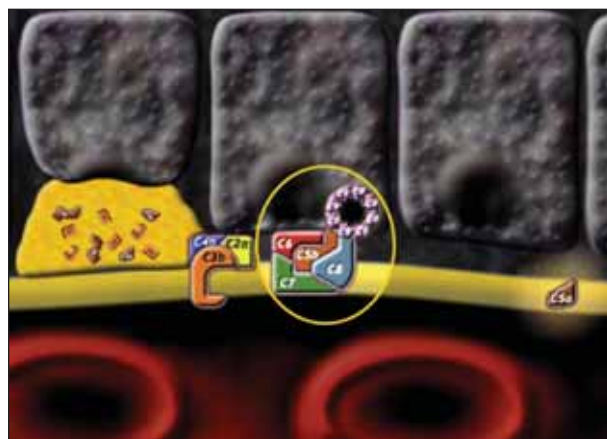


Figure 2. C5b is involved in the formation of membrane attack complex (MAC: C5b-9), which initiates cells lysis and has been shown to release proangiogenic molecules including PDGF and VEGF.

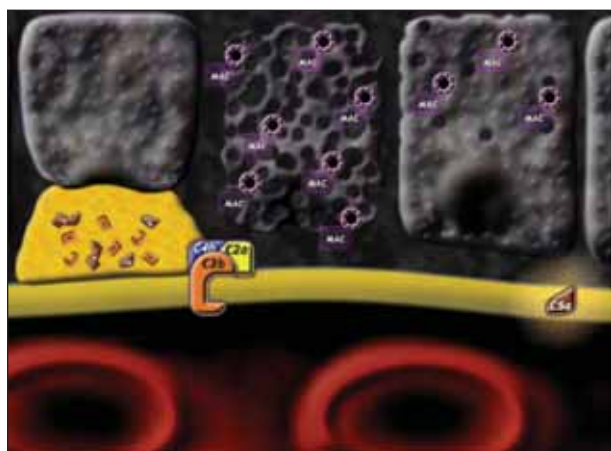


Figure 3. The MAC initiates lysis of RPE cells. Histopathologic specimens of human dry AMD lesions strongly stain for C5 and MAC at the key sites of pathology.

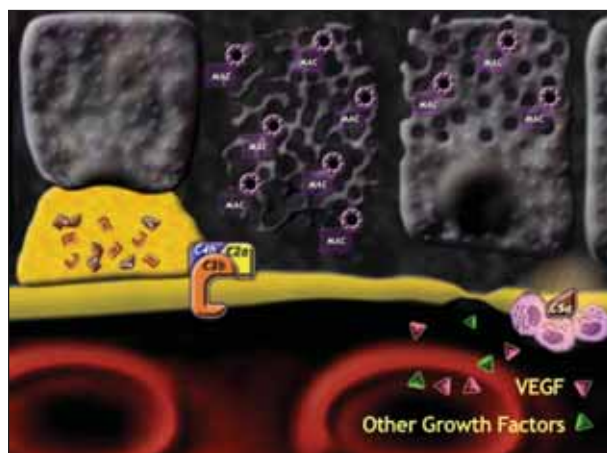


Figure 4. The C5a fragment is proinflammatory and stimulates the production of VEGF and other growth factors.

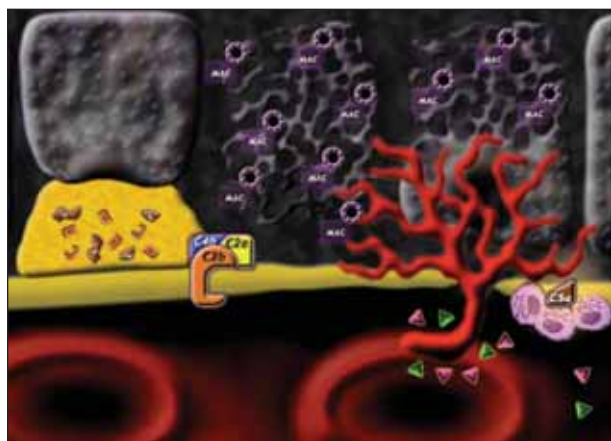
C5b, C6, C7, C8, and C9, forms a transmembrane channel within cells leading to osmotic lysis (Figures 1-5).<sup>6-8</sup>

The complement system is regulated by several proteins (complement control proteins), including CD35, CD46, and complement factor H. These proteins help the complement system regulate itself to keep the complement system from damaging host tissue while simultaneously directing the complement system to defend against harmful pathogens. Complement factor H mainly helps regulate the alternate pathway of the complement system.

Conditions involving genetic deficiencies in the complement system can lead to sepsis, extensive morbidity, and death. However, overactivation of the complement system can also be highly detrimental to host tissue. It is important to realize the duality of the complement system: when functioning appropriately, the complement system can have a highly protective effect against pathogens;

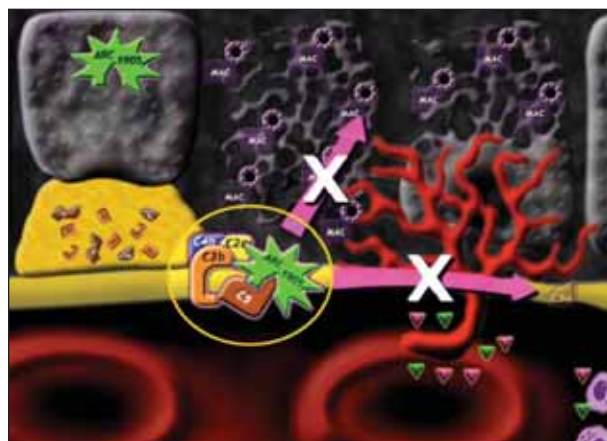
however, when the complement system is not regulated appropriately, extensive cellular damage to host tissue can occur.

Components of the complement system have been clearly shown to be present in the vitreous of human eyes. Furthermore, complement levels have been shown to be increased in patients with active inflammation and/or vitritis.<sup>9</sup> Components of the complement cascade and MAC have been found to be present in drusen.<sup>10</sup> Evidence of complement-mediated inflammation in AMD is further reinforced by multiple genetic linkage and association studies, suggesting that polymorphisms in genes coding for the complement regulatory proteins may account for approximately 50% to 75% of AMD cases and may increase the likelihood of AMD 7.4 to 10 times.<sup>11</sup> Preclinical laser-induced choroidal neovascularization (CNV) models have



**Figure 5.** VEGF and growth factors stimulated by C5a promote angiogenesis (CNV).

implicated complement activation as well. In experimental CNV formation, MAC: C5b-9 has been shown to be important.<sup>12</sup> Inhibition of the alternate pathway of complement activation led to decreased proangiogenic factors and decreased CNV formation in experimental CNV.<sup>13</sup> Taken together, there is strong support for complement-mediated disease in wet and dry forms of AMD.



**Figure 6.** By inhibiting C5-mediated inflammatory and MAC activities, therapeutic benefit may be achieved in both dry and wet AMD while sparing the immunoprotective functions of the complement system (C3b).

#### ARC1905

One promising approach to blocking the complement system in AMD is via the utilization of ARC1905 (Ophthotech, Inc., Princeton, NJ), a potent and selective inhibitor of factor C5 of the complement system. C5

**TABLE 1. INCLUSION AND EXCLUSION CRITERIA FOR THE PHASE 1 ARC1905 STUDY**

#### Inclusion Criteria

- Subfoveal choroidal neovascularization (CNV) due to AMD (predominately classic, minimally classic, or occult with no classic) as documented by fluorescein angiogram

#### Exclusion Criteria

- Previous or concomitant therapy with intravitreal corticosteroids
- Any of the following underlying diseases including:
  - Diabetic retinopathy
  - History or evidence of severe cardiac disease (e.g., NYHA Functional Class III or IV), history or clinical evidence of unstable angina, acute coronary syndrome, myocardial infarction or revascularization within last 6 months, ventricular tachyarrhythmias requiring ongoing treatment
  - History or evidence of clinically significant peripheral vascular disease, such as intermittent claudication or prior amputation
  - Clinically significant impaired renal (serum creatinine >2.5 mg/dl or s/p renal transplant or receiving dialysis) or hepatic function. Patients with results outside these ranges may be enrolled in consultation with Ophthotech
  - Stroke within 12 months of trial entry
  - Any major surgical procedure within 1 month of trial entry
  - Previous therapeutic radiation in the region of the study eye
  - Any treatment with an investigational agent in the past 60 days for any condition
  - Women who are pregnant or nursing
  - Known serious allergies to the fluorescein dye used in angiography, to the components of the ranibizumab formulation, or to the components of the ARC1905 formulation.

(from clinicaltrials.gov - NCT00709527)

ARC1905 shows great promise for enhanced efficacy in eyes with wet AMD in this large and expanding population.

inhibition prevents the formation of the key terminal fragments responsible for tissue pathology, C5a and the MAC (Figure 6). As mentioned above, C5a is proinflammatory, while the MAC initiates cell lysis and releases proangiogenic molecules (eg, platelet-derived growth factor [PDGF] and vascular endothelial growth factor [VEGF]). Histopathologic specimens of human dry AMD lesions strongly stain for C5 and MAC at the key sites of pathology. ARC1905 spares the formation of upstream complement components such as C3b, which are important in host defense mechanisms. By inhibiting C5-mediated inflammatory and MAC activities, therapeutic benefit may be achieved in both dry and wet AMD while sparing the immunoprotective functions of the complement system.

## PHARMACOLOGIC BLOCKADE OF THE COMPLEMENT SYSTEM

Ophthotech has completed a phase 1 trial (NCT00709527) examining the use of ARC1905 in patients with exudative AMD in combination with ranibizumab (Lucentis, Genentech). The study was an interventional, nonrandomized, noncontrolled, multicenter dose-escalation open-label safety study whose primary endpoint was to determine the presence of any dose-limiting toxicity. Safety endpoints included adverse events, vital signs, ophthalmic variables, and outcomes over a period of 6 months. Inclusion and exclusion criteria for the phase 1 ARC1905 study are provided in Table 1.<sup>14</sup>

Results of the phase 1 study were presented in April 2010 at the Association for Research in Vision and Ophthalmology 2010 Annual Meeting. Forty-three patients with subfoveal neovascular AMD received six monthly administrations of ARC1905 (0.3, 1, or 2 mg) in combination with ranibizumab (0.5 mg). Best corrected visual acuity in the study eye was 20/63 to 20/200. Dose escalation of ARC1905 was completed without any evidence of dose-limiting toxicity. Secondary endpoints included visual acuity and optical coherence tomography (OCT). Complement-associated single nucleotide polymorphism analysis was also conducted in a cohort of patients. The mean change in visual acuity at week 24 was an increase of +13.6, +11.7, and +15.3 letters at the doses of 0.3 mg, 1 mg, and 2 mg, respectively. Furthermore, 46%, 47%, and 60% percent of patients

gained 3 or more lines of visual acuity at the doses of 0.3 mg, 1 mg, and 2 mg, respectively. The mean change in OCT center point thickness was -150  $\mu$ m. The phase 1 study demonstrated that the combination of C5 and VEGF inhibition in neovascular AMD was well tolerated without evidence of acute toxicity.<sup>15</sup>

## IMPLICATIONS OF THE PHASE 1 ARC1905 STUDY AND CONCLUSIONS

The phase 1 ARC1905 study demonstrated that the combination of PDGF and VEGF inhibition was well tolerated, with an absence of dose-limiting toxicity. ARC1905 shows great promise for enhanced efficacy in eyes with wet AMD in this large and expanding population. Furthermore, the strong science of complement inhibition in dry AMD may translate into the first pharmacotherapy for this disease, which represents an enormous market with more than 16 million Americans and Europeans affected. A study evaluating the use of ARC1905 in patients with nonexudative AMD is in progress. ■

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- Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. *N Engl J Med*. 2008;358(24):2606-2617.
- Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. *Science*. 2005;308:385-389.
- Edwards AO, Ritter R, 3rd, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. *Science*. 2005;308:421-424.
- Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. *Science*. 2005;308:419-421.
- Gehrs KM, Jackson JR, Brown EN, Allikmets R, Hageman GS. Complement, age-related macular degeneration and a vision of the future. *Arch Ophthalmol*. 2010;128(3):349-358.
- Walport MJ. Complement. First of two parts. *N Engl J Med*. 2001;344(14):1058-1066.
- Walport MJ. Complement. Second of two parts. *N Engl J Med*. 2001;344(15):1140-1144.
- Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses. *Cell Res*. 2010;20(1):34-50.
- Mondino BJ, Sidikaro Y, Sumner H. Anaphylatoxin levels in human vitreous humor. *Invest Ophthalmol Vis Sci*. 1988;29(7):1195-8.
- Wang L, Clark ME, Crossman DK, et al. Abundant lipid and protein components of drusen. *PLoS One*. 2010;5(4):e10329.
- Gold B, Merriam JE, Zernant J, et al. Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. *Nat Genet*. 2006;38:458-62.
- Bora PS, et al. Role of complement and complement membrane Attack complex in laser-induced choroidal neovascularization. *J Immunol*. 2005;174:491-497.
- Bora NS, et al. Complement activation via alternative pathway is critical in the development of laser-induced choroidal neovascularization: role of factor B and factor H. *J Immunol*. 2006;177(3):1872-1878.
- ARC1905 (ANTI-C5 APTAMER) given either in combination therapy with Lucentis® 0.5 mg/eye in subjects with neovascular age-related macular degeneration. <http://www.clinicaltrials.gov/ct2/show/NCT00709527?term=NCT00709527&rank=1>. Accessed July 13, 2010.
- Targeting complement factor 5 in combination with vascular endothelial growth factor (VEGF) inhibition for neovascular age related macular degeneration (AMD): results of a phase 1 study. <http://www.abstractsonline.com/Plan/ViewAbstract.aspx?mID=2511&sKey=c47c76c1-a90e-4226-bc53-2686e5d1f306&cKey=5606acd6-5fb2-4bf3-8696-c51c44e1f836&mKey={1EA90E66-C548-49E0-9F05-30DA7938D511}>. Accessed July 13, 2010.