ORIGINAL ARTICLE

The Role of the Complement System in Age-Related Macular Degeneration

Bernhard H. F. Weber, Peter Charbel Issa, Diana Pauly, Philipp Herrmann, Felix Grassmann, Frank G. Holz

SUMMARY

Background: Age-related macular degeneration (AMD) is a common retinal disease in older people. In Europe, about 1.6% of persons over age 65 and more than 13% of persons over age 85 have late-stage AMD, which can severely impair vision. The development of AMD is influenced both by environmental factors and by a strong hereditary component.

Methods: We selectively searched the PubMed database for articles published between April 2001 and November 2013 with the key words “age-related macular degeneration,” “risk factor,” “complement,” and “therapy.” The website www.clinicaltrials.gov was also used to search for relevant clinical trials.

Results: Old age and smoking are confirmed risk factors for AMD. Moreover, genetic association studies have pointed to signaling pathways in which the complement system, a part of the individual’s innate immune system, takes on a central role in the pathogenesis of the disease. Several clinical trials designed to interfere specifically with these pathomechanisms have yielded rather disappointing results, although a phase II study of the monoclonal antibody lampalizumab showed that blocking complement factor D lessened the progression of geographic atrophy. A risk model based on 13 genetic markers was found to have positive predictive values in predisposed individuals that ranged from 5.1% (in persons aged 65 to 69) to 91.7% (in persons aged 85 or older). It should be borne in mind that 50% of patients with AMD are not carriers of risk-associated markers.

Conclusion: There is no rationale at present for genetic testing to estimate the individual risk of developing AMD. Several recent clinical trials have incorporated current pathophysiological knowledge, but nearly all of these trials have yielded negative findings, with only one exception.

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Age-related macular degeneration (AMD) is a late-onset, progressive disease of the central retina. In western, industrialized countries, it is the most common cause of irreversible loss of vision after the age of 55 years. Increasing age is associated with an increase in cases of AMD in all ethnic groups (1). Individuals of European origin have by far the highest AMD frequency, followed by Asians, Latin Americans, and Africans. The prevalence of late forms of AMD in Europe, Australia, and the USA is approximately 1.6% (over the age of 55 years), rising to more than 13% in those aged over 85 years (2). A further increase in prevalence is to be expected as a result of demographic changes (3).

AMD can be classified into an early and a late form. The early form often begins slowly and may remain asymptomatic. Patients’ first symptoms may be reduced visual acuity, nonspecific blurred vision, and later also distorted vision. Clinical examination during the early stage typically shows focal extracellular deposits (drusen) under the retinal pigment epithelium in the central region of the retina (the macula) (*Figure 1a*) (4).

AMD can progress to the late form, which if left untreated leads to loss of central visual acuity and loss of central vision (4). This often results in difficulties in reading, face recognition, or independent living, for example. Peripheral vision, and thus the ability to orient oneself, is usually retained.

The late form can manifest as either an atrophic form (“dry” form; geographic atrophy) (*Figure 1b*) or a neovascular (“wet”) form (*Figure 1c*). It is also possible for both forms to be present simultaneously in the same eye (4). In the active neovascular form functional loss usually occurs within days to weeks, while the atrophic form progresses slowly, over several years, but is not restricted to the macular area.

The only therapeutic approach to reduce the risk of progression to the late form of AMD is currently the use of certain food supplements (vitamin E, vitamin C, zinc, and beta-carotene or lutein/zeaxanthin). However, this has only been shown to be effective for patients with an advanced early form (intermediate AMD); in these patients, the risk of progression to a late form is reduced by up to 25% (5). This treatment is no longer effective if late AMD has already developed, according to the AREDS trials. The evidence in favor of this treatment was assessed as moderate by a Cochrane Review

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Figure 1: Clinical manifestation of age-related macular degeneration. Imaging of the ocular fundus (left) and high-resolution optical coherence tomography (OCT) (right) of (a) early and (b, c) late AMD (b: geographic atrophy [GA], c: choroidal neovascularization [CNV]). The dashed line indicates the location of the OCT section. 1 = photoreceptor layer, 2 = retinal pigment epithelium (RPE). (a) Ocular fundus imaging shows multiple drusen on the fundus (yellowish deposits beneath the RPE at Bruch's membrane), the typical manifestation of early dry AMD. OCT reveals drusen as deposits beneath the RPE (= 3). (b) The arrows indicate a central area of sharply delineated atrophy with loss of RPE and photoreceptor cells; this is also shown on the OCT (= 4). This atrophy is accompanied by complete loss of function in the affected area. (c) The final stage of neovascular AMD is subretinal scarring with degeneration of photoreceptors, RPE, and choroid membrane in the affected area. No retinal function is preserved in scarred areas.

in 2012 (5). A follow-up study involving more than 4200 participants showed no further benefit for administration of omega-3 fatty acids and lutein/zeaxanthin. However, the data prompted discussion of the possibility of replacing beta-carotene with lutein/zeaxanthin (6, 7). Beta-carotene had been established as a risk factor for lung cancer in smokers and former smokers. Taking vitamin E also seems to increase the risk of prostate cancer (8).

In recent years, repeat application of inhibitory antibodies against vascular endothelial growth factor (VEGF) into the vitreous has become the first-line treatment for patients with active neovascular AMD (4). This effective treatment is also used in other macular diseases with secondary choroidal neovascularization, such as high myopia and pseudoxanthoma elasticum. However, it fails to achieve any improvement if irreversible degeneration of the photoreceptors or other structures has already occurred (9).

For geographic atrophy there is no therapy yet available, although several therapeutic approaches are currently being tested in preclinical and clinical trials (10, 11). The development of future effective therapies for AMD may be fostered by an in-depth understanding of its complex pathogenesis and the identification of relevant metabolic pathways.

Risk factors

AMD is a complex, multifactorial disease with demographic, environmental, and genetic risk factors contributing to disease development (12, 13). The strongest demographic factor in the development of AMD is age. Smoking is also a highly significant environmental factor (odds ratio [OR] for smokers: 3.11; OR for former smokers: 1.34) (2). No further individual risk factors have been established.

The heritability of AMD, i.e. the relative contribution of genetic and non-genetic factors to the

phenotype, is estimated at a relatively high value of between 45% and 70% (14). Recent genome-wide association studies (GWASs) and an international multicenter meta-analysis involving more than 18 individual GWAS datasets, which combined included more than 17 000 cases of AMD and 60 000 control patients (15), contributed to defining an association between AMD and genetic variants in a total of 19 chromosomal regions (*eTable 1*). Unusually strong effects (high odds ratios) for a complex disease were found for loci on chromosome region 1q32, which carries the gene for complement factor H (CFH) (16–18), and on chromosome region 10q24, which includes the *ARMS2/HTRA1* genes (19, 20). Such genetic findings make it possible to establish, for the first time, a causal relationship between the development of AMD and a range of biological signalling and metabolic pathways. This is particularly true of the complement system of innate immunity, but also of the atherosclerosis signal pathway, collagen/extracellular matrix metabolism, and controlled cell death (apoptosis) (*eTable 1*) (15). This may give rise to as yet unknown possibilities for use for both genetic risk prediction and targeted development of novel therapies.

The significance of genetic findings for risk prediction

Genetic testing is not currently part of standard AMD diagnosis or treatment. However, many genetic risk variants with partly strong effects were found to be associated with the development of AMD and explain between 15% and 65% of the genetic risk (15). Due to its high genetic risk, AMD is a textbook case for the genetic risk calculation of a complex disease.

Several studies have modelled the risk of AMD on the basis of genetic and clinical risk factors. A measure of the value of such predictions is the area under the curve (AUC) for a receiver operating characteristic (ROC) curve. An ROC curve describes the true positives (sensitivity) versus the false positives (1 – specificity), in other words the accuracy with which it can be predicted whether or not an individual will develop the disease. A perfect risk model would have values of 100% for both sensitivity and specificity, and an AUC of 1.0. In practice, however, such values are difficult to achieve. For example, Grassman et al. (21) developed a risk model based on 13 common genetic risk variants for AMD with an AUC of 0.82. This model describes five risk groups, according to which almost half of all patients with late AMD fall into risk categories 4 and 5 and thus have a significantly higher genetic risk profile. Half of all AMD patients could potentially be predicted using this model, with a positive predictive value of between 5.1% (age group 65 to 69 years, risk group 4) and 91.7% (age group 85 years and above, risk group 5). The model can also predict approximately 50% of controls, with negative predictive values of 96.3% to 99.9%. However, 50% of AMD patients are in risk groups 1 to 3, so for these patients it must be assumed that the cause of their disease cannot be explained by

the known common genetic factors. The inclusion of nongenetic factors such as smoking and age nevertheless provided no significant improvement over purely genetic models (22–24).

The identification of additional genetic risk variants for AMD, including rare ones, will be an important factor in improving the predictive power of current risk models. For example, a rare protein-encoding variant of the *CFH* gene (*Arg1210Cys*) was found 40 times among 2423 AMD patients but only once among 1122 control individuals (25). This corresponds to an odds ratio of approximately 18 and can explain approximately 1% of the genetic variance. Disease onset was significantly (up to 6 years) earlier in carriers of the *Arg1210Cys* gene variant than in AMD patients without such a variant. There are probably other rare gene variants associated with AMD. Including this additional genetic information should make it possible to improve existing risk models and thereby increase the explained proportion of genetic variance.

Therapeutic complement cascade modulation

Neovascular AMD is already successfully treated using anti-VEGF drugs (ranibizumab and aflibercept approved by the FDA and EMA; bevacizumab in off-label use) (26). New drug development is therefore of great interest for treatment of geographic atrophy. A number of such AMD drugs are currently being tested in clinical (*Table*) and preclinical (*eTable 2*) trials, based on the assumption that systemic or local therapeutic modulation of complementation activation is of great significance for disease outcome.

The complement cascade is a soluble part of the innate immune system. Three different complement pathways activate enzyme cascades that ultimately lead to cell death (*eFigure*). There is also generation of inflammatory, chemotactic proteins that trigger inflammation (C3a, C5a) and opsonizing proteins that attract other immune cells (C3b). The complement system can be modulated by various classes of drugs; all levels of the cascade can be influenced.

The local neuroprotective anti-inflammatory effect of substances such as tandospirone, a serotonin receptor agonist, is being researched (*eFigure, Table, eTable 2*). In contrast, protein-binding and protein-inhibiting substances such as antibodies (LFG316, FCFD4514S, eculizumab), peptides (POT-4), and aptamers (ARC1905) have a targeted effect on one component of the complement system (e.g. C3, C5, CFD). A number of these clinical studies have been ended early as a result of disappointing interim results, and others with no reason reported (*Table*). In contrast, according to the first data published in advance, the antibody fragment lampalizumab shows promising effects in blocking complement factor D in a phase II trial. The option of genetic therapies that lead to the expression of complement-regulating proteins (e.g. CD46, CD59), and injection of recombinant proteins (e.g. C1-INH, sCR1, CFH), are being investigated in

TABLE

Complement system-modulating treatments for age-related macular degeneration (AMD) (clinical trials)

No. ^{*1}	Name (clinical trial phase)	Form	AMD type	Trial no. (NCT)	Status	Effect
1	Tandospirone/ AL-8309B (Phase III)	Serotonin 1A receptor agonist	GA	00890097	Ended in 2012 with no further reasons reported	Reduction in complement deposits
2	POT- 4/AL-78898A7/ Compstatin (Phase I/II)	Compstatin derivative	Neovascular AMD	00473928	Ended in 2010: 93% of patients showed no improve- ment in visual acuity (e1), no drug-related toxicity (39)	C3 block
			GA	01603043	Ended early in 2012 with no further reasons reported	
3	Eculizumab/ Soliris (Phase II)	Monoclonal antibody	GA	00935883	Ended in 2013: no improvement in average visual acuity or GA region in first 6 months, no reduction in drusen (e1, e2, e3)	C5 block
4	ARC1905 (Phase I)	Aptamer	Neovascular AMD	00709527	Ended in 2011 with no further reasons reported	C5 block
				00950638	Ended in 2012: No dose-dependent toxicity, improve- ment in visual acuity +10.2, change in central macular strength -124 μm^3 ^{*2}	
5	LFG316 (Phase II)	Antibody fragment (Fab)	Neovascular AMD	01535950	Ended in 2013 with no further reasons reported	C5 block
6	Lampalizumab (Phase II)	Antibody fragment (Fab)	GA	01602120	Ended in 2013: trial shows reduction in GA progression using lampalizumab	Factor D block

^{*1} See also references in eFigure

^{*2} Cousins SW, Ophthotech Study Group: 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. ARVO Meeting 2010; Abstr. 51, p. 1251

GA: geographic atrophy; NCT: registration number in database at www.clinicaltrials.gov

preclinical trials (eFigure, eTable 2). These substances possess a wide range of targets and drugs.

Turning to personalized medicine, it is conceivable that future AMD treatments may depend on the patient's individual genetic risk profile, among other factors. Following genetic stratification, patients with an unfavourable genetic risk profile and thus the maximum expected benefit could be treated, whereas patients who are not expected to benefit due to their genetic profiles could be protected from potential adverse effects caused by treatment. For discussion of the advantages and disadvantages of personalized medicine, and its ethical and logistical problems, see (27–29).

Open questions on the clinical significance of known AMD risk variants

Recent molecular genetic findings (eTable 1) provide a basis for current and future clinical trials aiming to enhance systemic or local therapeutic modulation of complement activation for AMD (Table, eTable 2). The question in which disease stage complement regulation might achieve therapeutic effects remains open. Although it can be inferred from current evidence that there is a causal relationship between dysregulated complement activation and the development of AMD, for now it remains unclear whether progression from

early to late disease is influenced by the known risk factors for the development of AMD and thus the respective signalling pathways discussed here (24, 30–33). In addition, information on the interaction between genetic variants and environmental factors (gene–environment interaction), e.g. the use of food supplements, has not yet been satisfactorily established (31, 34). As a result treatment recommendations cannot as yet be modified on the basis of a particular genotype.

The role of complement activation in late forms of AMD is not yet known. On the one hand, complement variants seem to be equally important in the development of both late forms of AMD (35, 36). This is also true of AMD-associated variants of genes that are unconnected with the complement cascade. This means that additional genetic and/or environmental factors must determine whether a neovascular complication or geographic atrophy develops. On the other hand, neither an association between genetic variants in complement protein-encoding genes and progression of a pre-existing geographic atrophy (37) nor conclusive evidence of an effect on the efficacy of VEGF antagonists in treating neovascular AMD has been found (38).

On the basis of the currently available treatment regimen, molecular genetic testing of AMD does not provide any additional individual benefit.

Summary

A number of findings from immunological, genetic, and protein biochemical studies indicate that the complement system plays an essential role in the etiology of AMD. Genetically determined, pathologically increased systemic complement activation may have considerable impact on the aging macula as a *locus minoris resistentiae*, with multiple changes, including pathological deposits in the subretinal extracellular matrix. In addition, changes in complement proteins may have specific local effects, such as impairment of complement activation control in the region of the retinal pigment epithelium and the extracellular Bruch's membrane beneath it.

Pharmacological modulation of complement cascade processes must find a balance between the beneficial effect of complement activation inhibition and preservation of sufficient functional activity for physiologically necessary immune responses. This is particularly important in chronic diseases such as AMD, for which treatment is usually administered over long periods. Ideally, the pharmacological effect would modulate only complement cascade components that are dysregulated in AMD, with no substantial effects, particularly systemic effects, on other areas of complement regulation. In this context, however, the effect of individual components of the complement system on the development of AMD, phenotype, and disease progression appear not to have been sufficiently investigated to date. Exploration of mechanisms that affect disease progression, rather than only those that determine predisposition to disease development, would be an important step forward. Further research is also needed in order to clarify whether dysregulation of systemic or local complement activation, or both, is the main determining factor in the pathogenesis of AMD. Such studies might affect which type of drug administration (local or systemic) is preferred. In the eye, local application minimizes systemic side effects, as has already been shown very successfully in the case of anti-VEGF treatment for neovascular AMD.

Conflict of interest statement

Prof. Charbel Issa has received trial funding from Heidelberg Engineering and Novartis. He has received lecture fees and reimbursement of travel expenses from Novartis and Bayer.

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Grassmann, MSc has received reimbursement of conference fees and travel expenses from ProRetina Deutschland.

Prof. Holz has received consultancy and lecture fees from Acucela, Alcon, Allergan, Genentech, Novartis, Roche, Merz, Heidelberg Engineering, and Bayer. He has received reimbursement of travel expenses and conference fees from Roche, Novartis, Genentech, and Bayer. He has also received trial funding from Bayer, Novartis, Genentech, Acucela, and Pfizer.

Prof. Weber has received consultancy and lecture fees from and reimbursement of travel expenses from Alcon and Novartis.

Dr. Herrmann declares that he has no conflict of interests.

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KEY MESSAGES

- Specific genetic risk factors (e.g. *CFH*, *ARMS2/HTRA1*, *C3*, *CFI*) for the development of age-related macular degeneration (AMD) are known.
- Genetic testing for AMD is currently of no significance for diagnosis or treatment.
- The complement system plays a central, causative role in the pathogenesis of AMD.
- Complement system-modulating treatments are currently being investigated in preclinical and clinical trials.
- Anti-VEGF therapy is an effective, safe treatment for neovascular AMD.

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eFIGURE

Complement system and modulating drugs, preclinically and clinically. Drugs used to treat age-related macular degeneration (AMD) can be divided into three complement system activation pathways but also target the unifying, final enzyme complexes. Activation occurs via the classical (yellow, orange), lectin-dependent (red, orange), and alternative (blue, purple) pathways. The central stages (gray) involve enzyme complexes (convertases) that cleave C3 and C5. The final common pathway of the complement cascade leads to the formation of a terminal membrane attack complex in the cell (C5b-9), circulating anaphylatoxins (C3a, C5a), and opsonin (C3b). Complement regulators such as complement factor H (CFH) and complement factor I (CFI) prevent uncontrolled feedback loops. Complement components that are genetically associated with AMD are shown in bold and underlined. Target proteins for which treatments are being developed have been labelled using superscript figures that indicate further information on the drugs concerned (corresponding to the numbering in the *Table* [Text] and *eTable 2*). MBL: mannan-binding lectin; MASP: MBL-associated serine protease; FD: factor D; FB: factor B; P: properdin; CFH: complement factor H; CFI: complement factor I (Figure modified according to Khandhadia et al. [39])

eTABLE 1

Summary of common AMD-associated variants (modified according to [15])

SNP	Candidate genes in region	Biological process	Frequency of risk variant in AMD patients	Odds ratio	95% CI
rs10737680/A	<i>CFH</i>	Complement activation	64%	2.43	(2.39 to 2.47)
rs13081855/T	<i>COL8A1</i>	Extracellular matrix organization	10%	1.23	(1.17 to 1.29)
rs6795735/T	<i>ADAMTS9</i>	Extracellular matrix organization	46%	1.10	(1.07 to 1.14)
rs4698775/G	<i>CFI</i>	Complement activation	31%	1.14	(1.10 to 1.17)
rs429608/G	<i>C2/CFB</i>	Complement activation	86%	1.74	(1.68 to 1.79)
rs943080/T	<i>VEGFA</i>	Angiogenesis	51%	1.15	(1.12 to 1.18)
rs3812111/T	<i>COL10A1</i>	Extracellular matrix organization	64%	1.10	(1.07 to 1.14)
rs3130783/A	<i>DDR1</i>	Extracellular matrix organization	79%	1.16	(1.11 to 1.20)
	<i>IER3</i>	Regulation of inflammatory processes/apoptosis			
rs13278062/T	<i>TNFRSF10A</i>	Activation of NF-κB kinases/apoptosis	48%	1.15	(1.12 to 1.19)
rs334353/T	<i>TGFBR1</i>	Extracellular matrix organization/angiogenesis	73%	1.13	(1.10 to 1.17)
rs10490924/T	<i>HTRA1</i>	Extracellular matrix organization	30%	2.76	(2.72 to 2.80)
	<i>ARMS2</i>	Unknown			
rs9542236/C	<i>B3GALT1</i>	Protein glycosylation	44%	1.10	(1.07 to 1.14)
rs8017304/A	<i>RAD51B</i>	DNA repair/apoptosis	61%	1.11	(1.08 to 1.14)
rs920915/C	<i>LIPC</i>	Cholesterol/LDL/HDL metabolism	48%	1.13	(1.09 to 1.17)
rs1864163/G	<i>CETP</i>	Cholesterol/LDL/HDL metabolism	76%	1.22	(1.17 to 1.27)
rs2230199/C	<i>C3</i>	Complement activation	20%	1.42	(1.37 to 1.47)
rs4420638/A	<i>APOE</i>	Cholesterol/LDL/HDL metabolism	83%	1.30	(1.24 to 1.36)
rs5749482/G	<i>TIMP3</i>	Extracellular matrix	74%	1.31	(1.26 to 1.36)
	<i>SYN3</i>	Neurotransmitter secretion			
rs8135665/T	<i>SLC16A8</i>	Membrane transport	21%	1.15	(1.11 to 1.19)

AMD: age-related macular degeneration; SNP: single-nucleotide polymorphisms; CI: confidence interval; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; DNA: deoxyribonucleic acid; LDL: low-density lipoprotein; HDL: high-density lipoprotein

eTABLE 2

Complement system-modulating treatments for age-related macular degeneration (preclinical trials)

No.*	Name	Form	Effect
7	C1-INH	Protease inhibitor	Inhibition: C1q, C1r, C1s
8	TT30/CR2-FH	CFH and CR2 fusion protein	Blocking C3
9	TA106	Antibody fragment (Fab)	Blocking factor B
10	rCFH	CFH from human plasma or recombinant CFH	CFH replacement, blocking C3 convertase
11	AdCAGCD46	Gene therapy using human CD46	Blocking C4b and C3b
12	sCR1/CDX-1135/TP10	CR1	Blocking C4b and C3b
13	JPE-1375/JSM-7717	Peptide as C5aR antagonist	Binding C5a
14	PMX53	Peptide as C5aR antagonist	Binding C5a
15	AdCAGsCD59	Gene therapy using human CD59	Block of terminal membrane complex
16	670 nm light therapy	Physical	Anti-inflammatory

CFH: complement factor H; CR: complement receptor
 *See also reference in eFigure.