European Journal of Ophthalmology / Vol. 17 no. 6, 2007 / pp. 943-949

The effect of complement factor H Y402H polymorphism on the outcome of photodynamic therapy in age-related macular degeneration

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PURPOSE. *Photodynamic therapy (PDT) has been widely used in the treatment of age-related macular degeneration (AMD). The complement cascade has an important role in the tissue reactions occurring after PDT. The Y402H polymorphism of the complement factor H (CFH) gene has been identified as a risk factor for AMD. Since CFH is central in the regulation of the complement system the authors wanted to analyze whether the CFH Y402H polymorphism modifies the PDT outcome in AMD.*

METHODS. *A total of 88 patients having been treated with PDT and without further scheduled PDT sessions were analyzed. Depending on the situation at their final PDT session the patients were classified retrospectively as PDT-responders or PDT-nonresponders. All patients were genotyped for the CFH Y402H polymorphism.*

RESULTS. *The proportion of PDT-responders was 18/26 (69.2%) in patients homozygous for the CFH Y402H risk allele, 34/50 (68.0%) in heterozygous, and 7/12 (58.3%) in patients with the normal genotype (p=0.520). The median number of PDT treatments of the PDT-responders was three for all the genotypes.*

CONCLUSIONS. *The dysfunction of the CFH related to the risk of AMD and caused by the Y402H polymorphism does not modify the outcome of PDT. Genotyping for CFH Y402H cannot be used to select patients for this treatment. (Eur J Ophthalmol 2007; 17: 943-9)*

KEY WORDS. *Age-related macular degeneration, Complement factor H, Photodynamic therapy*

Accepted: June 12, 2007

INTRODUCTION

Photodynamic therapy (PDT) has been widely used in the treatment of exudative age-related macular degeneration (AMD). By damaging the endothelial cells and other structures in choroidal neovascular membranes, PDT induces photothrombosis of the choroidal neovascularization and normal vessels, followed by a varying degree of recovery and recanalization (1-4). The complement system is a powerful mediator of innate immunity which in addition to attacking foreign organisms affects many other cell biological functions, including those related to debris removal after tissue destruction (5, 6). The complement cascade has been shown to be a central element in the tissue response to experimental PDT (7, 8). Complement factor H (CFH) modulates complement activation especially on biological membranes (9) and the Y402H (1277T>C) polymorphism in the *CFH* gene carries an increased risk of AMD in many populations (10-20). Considering the central role of the complement system in PDT-generated tissue reactions we wanted to analyze whether the CFH Y402H polymorphism might be related to the outcome of PDT in patients with exudative AMD.

 1120-6721/943-07$15.00/0

METHODS

Patients

Included were one eye each of 95 patients with recent exudative AMD who underwent PDT at the Retina Clinic of the Department of Ophthalmology, Helsinki University Central Hospital, in 1999–2005. Written informed consent was obtained from all of the subjects after explaining the nature and possible consequences of the study. The study was approved by the Ethics Committee of the Helsinki University Eye and Ear Hospital and performed in accordance with the Declaration of Helsinki.

These patients belong to a larger group that has been previously used in a study of frequencies of the Y402H polymorphism of the complement factor H (CHF) gene in Finnish patients with AMD (n=335) (19). From this original patient group we identified a total of 95 patients who had been treated with PDT in 1999–2005 at the Department of Ophthalmology, Helsinki University Central Hospital. A total of seven PDT-treated patients with AMD were excluded from the final analysis: six patients were scheduled for further PDT sessions and one of the patients had been given an intravitreal injection of triamcinolone acetonide.

If a patient had bilateral exudative AMD, the eye that had PDT therapy for the first time at a date closest to March 31, 2003, was selected as the study eye. Thus, the final material consisted of 88 PDT-treated eyes in which no further PDTs were planned (Tab. I).

Ophthalmologic investigations

Visual acuity (VA) assessment using Snellen or Early Treatment Diabetic Retinopathy Study (ETDRS) tables and transformed into logMAR values, biomicroscopy of the anterior and posterior parts of the eye, and fluorescein angiography (FA) were performed in all patients (Topcon Imagenet [Topcon Inc., Tokyo, Japan] or Heidelberg retinal angiograph [Heidelberg Engineering; Heidelberg, Germany] systems). The choroidal neovascularization (CNV) category was further classified into lesions where the CNV lesion was ≥50% of the total lesion area. These lesions were graded as predominantly classic, minimally classic, or occult according to the Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) study guidelines (21). The treatment decisions were made by retina specialists at the Department of Ophthalmology, Helsinki University Hospital (P.T., P.R., and I.I.), mostly based on guidelines set by the Visudyne studies (22).

The records and the angiograms of the patients were later reviewed by a retina specialist (I.I.) masked to the identity and the CFH Y402H genotype of the patients. Lesion sizes were measured from the digital angiograms using the software of the corresponding imaging systems. Lesion size included the occult and classic choroidal neovascular lesion components, serous pigment epithelial detachment (PED), and hemorrhage, dense enough to cover underlying fluorescence. The patients were classified as PDT-responders or PDT-nonresponders based on the outcome of PDT after the last treatment session. In the PDT-responders the PDT treatment was considered to be successful (anatomic response), if the treating physician had deemed the lesion to be clinically dry without active leakage from CNV in FA at a visit scheduled at least 12 weeks after the last PDT treatment. In the PDT-nonresponders the PDT sessions had been discontinued by the treating retina specialist due to a still exudative lesion after several PDT sessions. Our clinic is the only referral

TABLE I - PATIENT DEMOGRAPHY, ALL EYES

	Genotype (CFH Y402H)					
Characteristic	**CC, n=26**	**CT, n=50**	**TT, n=12**	**CC or CT, n=76**	**All genotypes, n=88**	**p**
Age, yr, mean (SD)	73.7 (7.4)	75.8 (6.0)	75.7 (5.9)	75.1 (6.5)	75.2 (6.4)	0.634*
Percent female	84.6	72.0	75.0	76.3	76.1	1.000†
Lesion size (mm^2), median (interquartile range)	5.07 (9.01)	6.06 (9.78)	6.35 (6.29)	5.69 (8.99)	5.79 (8.39)	0.392*

*Kruskal-Wallis H-test, within different genotypes.
†Fisher exact test, TT compared with CT or CC.
CFH = Complement factor H

center for patients with AMD in the district where the patients came from.

PCR sequencing

DNA were extracted from 10 mL of peripheral blood using a phenol-chloroform method. The DNA of the study subjects was amplified by the polymerase chain reaction (PCR) and sequenced using primers forward 5'-ctttgttagtaactttagttcg-3' and reverse 5'-ttagaaagacatgaacatgctagg-3' to determine the T1277C genotypes. Sequencing was performed using cycle sequencing with the Big Dye Terminator kit (version 3.1) supplied by Applied Biosystems (ABI, Foster City, CA, USA), and reactions were run on an ABI 3730 capillary sequencer according to the manufacturer's instructions.

Statistical analysis

All analyses were performed with SPSS (SPSS Inc., Chicago, IL, USA; release 13.0; 2005) statistical software. Differences between groups were evaluated by Mann-Whitney *U*-test, Kruskal-Wallis H-test (continuous variables), the Fisher exact test, and the chi square test. The median and the interquartile range are given as descriptive statistics. The level of significance was chosen as $p<0.05$.

Power analysis was performed with the power calculator at http://calculators.stat.ucla.edu/powercalc/. With the PDT response rate of one group at 50% it was estimated that with the sample size used a difference of 30 absolute percent units could be observed in relation to another group with the probability of 0.05 and power of 0.8.

RESULTS

The mean age (SD) of the patients was 75.2 (6.4); 67/88 (76.1%) of the patients were female. Of patients homozygous for the complement factor H gene risk allele (CC) 18/26 (69.2%) were PDT-responders. The corresponding proportions were 34/50 (68.0%) and 7/12 (58.3%) in patients heterozygous for the Y402H polymorphism (CT) and in those with the normal genotype (TT), respectively ($p=0.520$, Fisher exact test, TT compared to CT or CC). Of all the 88 lesions analyzed 59 (67.0%) were successfully inactivated. Response to PDT in different lesion categories is shown in Table II. There was no significant difference in response rates to PDT treatment between genotypes within lesion type categories. In occult lesions the PDT-responder eyes with the CC genotype had received

TABLE II - RESPONSE TO PHOTODYNAMIC THERAPY WITHIN CHOROIDAL NEOVASCULARIZATION (CNV) CATEGORIES (eyes with the CNV lesion <50% of the total lesion area excluded) IN THE DIFFERENT GENOTYPES OF THE COMPLEMENT FACTOR H (CFH) GENE Y402H POLYMORPHISM

	Genotype (CFH Y402H)					
	CC	**CT**	**TT**	**CC or CT**	**All genotypes**	**p**
Predominantly classic CNV lesion, n	8	23	4	31	35	
Patients with an anatomic response, n (%)	6 (75.0)	17 (73.9)	3 (75.0)	23 (74.2)	26 (74.3)	1.00*
Number of treatments in responders, median (interquartile range)	3.0 (2)	3.0 (2)	4.0 (–)	3.0 (2)	3.0 (2)	0.25†
Minimally classic CNV lesion, n	9	13	2	22	24	
Patients with an anatomic response, n (%)	5 (55.6)	9 (69.2)	0 (0)	14 (63.6)	14 (58.3)	0.163*
Number of treatments in responders, median (interquartile range)	4.0 (3)	3.0 (2)	—	3.0 (2)	3.0 (2)	0.483†
Occult CNV lesion, n	6	9	5	15	20	
Patients with an anatomic response, n (%)	4 (66.7)	7 (77.8)	4 (80.0)	11 (73.3)	15 (75.0)	1.00*
Number of treatments in responders, median (interquartile range)	3.5 (3)	1.0 (1)	2.0 (2)	2.0 (2)	2.0 (2)	0.028†

*Fisher exact test, TT compared with CT or CC.
†Kruskal-Wallis H-test

somewhat more treatments than those with the CT genotype (p=0.012, Mann-Whitney *U*-test).

Median number of PDT sessions of the PDT-responders was three in all the genotypes. In all the PDT-responders the median (interquartile range) number of PDT treatments was 3.0 (2) and in all the PDT-nonresponders it was 2.0 (1) (p=0.048, Mann-Whitney *U*-test) (Tab. III).

To exclude a possible bias produced by a various number of PDT sessions we also performed an analysis of CFH Y402H genotypes comparing the PDT-respoders with ≤2 or ≤3 PDT sessions with PDT-nonresponders with ≥2 or ≥3 PDT sessions, respectively. No difference existed in CFH Y402H genotype distribution between the PDT-responders and PDT-nonresponders (Tab. IV).

A statistically significant difference existed in final VA (p<0.001) and in change in VA (p<0.001) between all the PDT-responders and all the PDT-nonresponders. PDT-responders with the CC genotype appeared to have somewhat better final VA than the patients with the CT genotype (p=0.020, Mann-Whitney *U*-test), but generally no difference was detected in the final VA or in change of VA in the PDT-responders or the PDT-nonresponders between different genotypes (Tab. V).

Logistic regression analysis was performed with the presence of anatomic response to PDT as a dependent variable. Covariates were age, sex, smoking, lesion size, Y402H genotype, and lesion configuration. None of the variables was selected in the model.

TABLE III - NUMBER OF PHOTODYNAMIC THERAPY (PDT) TREATMENTS OF THE PDT-RESPONDERS AND PDT-NONRESPONDERS

	Genotype (CFH Y402H)					
	CC	**CT**	**TT**	**CC or CT**	**All genotypes**	**p**
Median number of PDT treatments in PDT-responders (interquartile range)	3 (2)	3 (2)	3 (3)	3 (2)	3 (2)	0.311*
Median number of PDT treatments in PDT-nonresponders (interquartile range)	3 (2)	2 (2)	2 (4)	2 (1)	2 (1)	0.098*

*Kruskal-Wallis H-test

TABLE IV - GENOTYPES OF PHOTODYNAMIC THERAPY (PDT)-RESPONDERS WITH ≤2 OR ≤3 PDT TREATMENTS COMPARED TO PDT-NONRESPONDERS WITH ≥2 OR ≥3 PDT TREATMENTS

Genotype (CFH Y402H)	**PDT-responders, ≤2 PDT sessions**	**PDT-nonresponders, ≥2 PDT sessions**	**p**
CC	4 (22)	8 (35)	0.406*
CT	13 (68)	11 (48)	
TT	2 (10)	4 (17)	
Total	19	23	
	≤3 PDT sessions	**≥3 PDT sessions**	
CC	10 (25)	6 (50)	0.182*
CT	25 (63)	4 (33)	
TT	5 (12)	2 (17)	
Total	40	12	

Values are n (%). Percent indicates the ratio of PDT-responders or PDT-nonresponders within each genotype.
*Chi-square test

DISCUSSION

In our study, no overall difference existed in response to PDT between different genotypes of the complement factor H gene Y402H polymorphism. Otherwise, our results resemble later studies on PDT treatment with less treatment sessions needed on average (23) than in the TAP and VIP studies (21, 24). Recently, Goverdhan et al (25) analyzed visual loss after PDT in relation to the CFH Y402H genotype. They reported that in their 27 eyes treated with PDT, 13 eyes with the CC genotype experienced a larger loss of visual acuity than the 2 eyes with the TT genotype. Such a difference was not confirmed in our study where the losses of visual acuity were in general evenly distributed between the genotypes. The primary aim of our study was to evaluate the impact of the CFH Y402H polymorphism on chorioretinal tissue reactions in exudative AMD, using PDT as an experimental model. Analyzing visual results after PDT in-depth would require much larger materials with extended follow-ups. It should be remembered, however, that AMD is a complex trait and also other observed risk factors (26-29) for the disease may in theory modify the response to PDT.

CFH polymorphism is a strong risk factor for AMD, the prevalence being rather similar in all subtypes of the disease (17, 30). The complement system is a cascade of enzymes operating as a vital part of innate immunity (5, 6). CFH is associated with regulation of the complement especially on biological membranes (9). The complement system is activated in experimental PDT, and the effect of PDT can be modified by complement activators or inhibitors (7, 8). The complement system has also recently been identified to have a role in CNV formation in an experimental murine model (31).

In the eye the mechanism of PDT is based on activation of verteporfin molecules attached to neovascular membrane endothelial cell walls. Subsequent release of free radicals from the drug leads to damage on endothelial cells and other structures in the neovascular and normal choriocapillaris vessels. A tissue response follows, clearing the cellular debris and revascularing the choriocapillaris (32). Such a sequence of events includes many phases in which CFH has an important regulatory role. In view of this background it was surprising that we were unable to show any clear effect of CFH polymorphism on the response to PDT treatment although the CFH Y402H is such a powerful risk factor for AMD.

The PDT response as used in this study is an an empirical variable possibly also reflecting other than biological factors. For instance, the patients' requests to halt further PDT sessions due to inconvenience of frequent visits is difficult to document in a retrospective study. The PDT response in this study was not planned to be used as a measure of maximal anatomic succes of PDT as a treat-

TABLE V - VISUAL ACUITIES (VA) IN PHOTODYNAMIC THERAPY (PDT)-RESPONDERS AND PDT-NONRESPONDERS IN THE DIFFERENT GENOTYPES OF THE COMPLEMENT FACTOR H (CFH) GENE Y402H POLYMORPHISM

	Genotype (CFH Y402H)					
	CC	**CT**	**TT**	**CC or CT**	**All genotypes**	**p**
PDT-responders, n	18	34	7	52	59	
Final VA, median logMAR (Snellen)	0.6 (20/80)	1.0 (20/200)	0.8 (20/125)	0.7 (20/100)	0.7 (20/100)	0.048*
Interquartile range logMAR	0.6 (6 lines)	0.9 (9 lines)	0.5 (5 lines)	1.0 (10 lines)	0.6 (6 lines)	
Change in VA, median logMAR (Snellen)	0.0 (0 lines)	–0.3 (–3 lines)	–0.3 (–3 lines)	–0.2 (–2 lines)	–0.3 (–3 lines)	0.563*
Interquartile range logMAR	0.6 (6 lines)	1.0 (10 lines)	1.0 (10 lines)	0.6 (6 lines)	0.6 (6 lines)	
PDT-nonresponders, n	8	16	5	24	29	
Final VA, median logMAR (Snellen)	1.5 (20/640)	1.3 (20/400)	1.3 (20/400)	1.3 (20/400)	1.3 (20/400)	0.740*
Interquartile range logMAR	1.1 (11 lines)	0.6 (6 lines)	1.1 (11 lines)	0.6 (6 lines)	0.6 (6 lines)	
Change in VA, median logMAR (Snellen)	–1.0 (–10 lines)	–0.8 (–8 lines)	–0.5 (–5 lines)	–0.9 (–9 lines)	–0.7 (–7 lines)	0589*
Interquartile range logMAR	1.3 (13 lines)	0.8 (8 lines)	0.7 (7 lines)	0.8 (8 lines)	0.7 (7 lines)	

A statistically significant difference exists in final visual acuity ($p<0.001$) and in change in visual acuity ($p<0.001$) between PDT-responders and PDT-nonresponders.
*Kruskal-Wallis H-test

ment modality. Although the retreatment rates in our patients were lower than those in the TAP and VIP studies, in accordance with later clinical studies (23), it is possible that with more PDT sessions some of the PDT-nonresponders would be transformed into PDT-responders. However, the analysis of CFH Y402H genotypes comparing PDT-responders with the same or smaller number of PDTs than respective PDT-nonresponders showed no difference in genotypes between the groups. The results of studies employing combination of PDT with intravitreal triamcinolone acetonide have shown a dramatic decrease in the number of PDT sessions needed (33). This indicates that with manipulation of the inflammatory process in AMD lesions the number of PDT treatments can be reduced. If the CFH Y402H polymorphism would have an effect of similar magnitude as triamcinolone acetonide on the PDT-response it would most likely have been found in the present study as a difference in genotypes between PDT-responders and PDT-nonresponders.

These findings and our observations speak to the view that Y402H polymorphism of the *CFH* gene causes a specific dysfunction of the molecule, possibly related to processing of drusenoid material, but the response to a more general type of chorioretinal damage is similar in patients with CFH Y402H polymorphism and in those with the normal type of the protein. These results also support the view that genotyping for CFH Y402H polymorphism cannot be used to select patients with AMD for PDT treatment.

ACKNOWLEDGEMENTS

Supported by grants from the Päivikki and Sakari Sohlberg Foundation, Helsinki; The Mary and Georg Ehrnrooth Foundation, Helsinki; The Eye and Tissue Bank Foundation, Helsinki; The Eye Foundation, Helsinki; The Evald and Hilda Nissi Foundation, Vaasa; and Helsinki University Central Hospital Research Funds (TYH5117, TYH6233), Finland.

The authors have no financial intrests to disclose.

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