Coagulation Gene Predictors of Photodynamic Therapy for Occult Choroidal Neovascularization in Age-Related Macular Degeneration

Francesco Parmeggiani,1 Ciro Costagliola,2 Donato Gemmati,3 Sergio D’Angelo,1 Paolo Perri,1 Claudio Campa,1 Linda Catozzi,3 Federica Federici,3 Adolfo Sebastiani,1 and Carlo Incorvaia1

PURPOSE. To determine whether different coagulation-balance genetic polymorphisms explain the variable clinical outcomes of photodynamic therapy with verteporfin (PDT-V) in Caucasian patients with occult subfoveal choroidal neovascularization (CNV) due to age-related macular degeneration (AMD).

METHODS. The clinical records of consecutive patients with AMD-related occult CNV, treated with PDT-V for evidence of disease progression, were retrospectively examined. Eighty-four eligible subjects were subdivided into responders and nonresponders based on CNV responsiveness to the first PDT-V over a 3-month period. Six gene polymorphisms (i.e., factor V G1691A, prothrombin G20210A, factor XIII-A G185T, methylenetetrahydrofolate reductase C677T, methionine synthase A2756G, and methionine synthase reductase A66G) were genotyped in each patient. Logistic regression analyses were performed to explore the predictive role of phenotypic and genotypic variables for PDT-V effectiveness.

RESULTS. Regression models documented that PDT-V nonresponders were more frequently patients with the hyperfibrinolytic G185T mutation of factor XIII-A (odds ratio [OR], 0.28; 95% confidence interval [CI], 0.11-0.73; P < 0.01). Univariate logistic regression was indicative of an overrepresentation of PDT-V responders among the combined carriers of thrombophilic factor V 1691A and prothrombin 20210A alleles (OR = 3.8; 95% CI: 0.94-15.6; P = 0.07). All the other predictors considered did not significantly influence the short-term CNV responsiveness to PDT-V.

CONCLUSIONS. These data provide evidence of the presence of a pharmacogenetic relationship between peculiar coagulation-balance genetic backgrounds and different levels of PDT-V effectiveness in patients with AMD with occult CNV. (Invest Ophthalmol Vis Sci. 2008;49:3100–3106) DOI:10.1167/iovs.07-1654

From the 1Department of Ophthalmology and the 3Department of Hematology, Study Center for Hemostasis and Thrombosis, University of Ferrara, Ferrara, Italy; and the 2Department of Health Sciences, University of Molise, Campobasso, Italy.

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Corresponding author: Francesco Parmeggiani, Sezione di Clinica Oculistica, Dipartimento di Discipline Medico-Chirurgiche della Comunicazione e del Comportamento, Università degli Studi di Ferrara, Corso Giovecca 203, 44100 Ferrara, Italy; francesco.parmeggiani@unife.it.

The occurrence of choroidal neovascularization (CNV) beneath the fovea is a common cause of central blindness or low vision in Caucasian individuals with age-related macular degeneration (AMD). Photodynamic therapy with verteporfin (PDT-V) and drugs acting against vascular endothelial growth factor (anti-VEGF) represent the most commonly used treatments for subfoveal AMD-related CNV. The combined use of both these strategies is the most promising therapeutic approach toward this harmful disease. In patients with AMD, the PDT-V benefit has been reported not only for predominantly classic CNVs, but also for selected cases of occult lesions without classic component. Particularly, PDT-V can be useful for the treatment of subfoveal occult CNV with evidence of recent progression and a lesion size ≤4 Macular Photocoagulation Study (MPS) disc areas (DAs). The therapeutic effect of PDT-V is achieved by a laser-light–induced thrombosis of CNV that has been photosensitized by the administration of verteporfin. The individually variable efficacy of standardized PDT-V is clearly noticeable reviewing the outcomes of Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP), Visudyne in Photodynamic Therapy (VIP), and Visudyne in Minimally Classic Choroidal Neovascularization studies. In fact, the rather proportioned percentage of cases with or without severe visual loss after PDT-V is evident for all the AMD-related forms of CNV and, especially, for occult neovascular lesions. Moreover, differences in CNV responsiveness to standardized PDT-V between Asian and Caucasian patients have recently been pointed out. Despite the evidence of individual and racial variabilities, the predictors of verteporfin therapy for occult CNV have been hitherto examined without considering the role of coagulation-balance genetic conditions in changing its effectiveness. Several gene mutations can affect the balance between pro- and anticoagulant mechanisms, accounting for the occurrence of thrombophilic or hemorrhagic diatheses. Although the well-known, therapeutic effect of PDT-V is based on a photochemical perturbation of the hemostasis and coagulation within the neovascular complex, only recently we have documented the presence of predictive correlations between peculiar coagulation-balance gene polymorphisms and different levels of PDT-V responsiveness in patients with AMD who have classic or predominantly classic CNV.

The purpose of this study was to investigate the predictive role of single nucleotide polymorphisms (SNPs) that encode enzymes involved in coagulation, fibrinolysis, and/or thrombosis in the extent of the benefit that will be realized by the application of standardized PDT-V in Caucasian patients with AMD, complicated by subfoveal occult CNV with no classic component. For this reason, we have examined the short-term variability of angiographic findings after the first PDT-V, considering its putative association with several common or uncommon gene variants, schematically shared in two typologies: (1) gain-of-function SNPs directly influencing the coagulation...
cascade: factor V Leiden (FVL-G1691A), prothrombin G20210A (FII-G20210A), and factor XIII A185T (FXIIIA-G185T),30–35; and (2) the SNPs that modulate homocysteine (Hcy) metabolism, which indirectly affects thrombocoagulative functionality: methylenetetrahydrofolate reductase C677T (MTHFR-C677T), methionine synthase A2756G (MS-A2756G), and methionine synthase reductase A66G (MTRR-A66G).36–38

METHODS

We conducted a retrospective analysis of the clinical records of 84 Caucasian patients affected by newly diagnosed, subfoveal, AMD-related occult CNV, who had been exclusively treated with standardized PDT-V. Diagnosis of exudative AMD was based on the International ARM Epidemiologic Study Group criteria.40 For the purposes of this study, patients with AMD were consecutively selected to achieve a study population affected by occult CNV, evidencing recent disease progression and a lesion size consistent with the TAP/VIP Study criteria.3 Within 1 week after angiographic examinations, according to the International Guidelines for the application of PDT-V, all photodynamic treatments were performed, labeled as a nonresponder to PDT-V (Fig. 1). When one or more of these signs of recovery were absent at the post-PDT-V examination, the patient was labeled as a nonresponder to PDT-V (Fig. 2). Both responders and nonresponders underwent re-treatments when needed, in accordance with the international guidelines for PDT-V application (TAP/VIP protocol).3

Inclusion and exclusion criteria are listed in Table 1. All patients gave written informed consent to participate to the study. The local ethics committee reviewed and approved the clinical trial. The study adhered to the tenets of the Declaration of Helsinki. Soon after the pre-PDT-V angiographies, three blood samples were collected for SNPs genotyping. In the course of retrospective data examination, patients with equal or decreased post-PDT-V GLD and area of CNV and concomitant CNV leakage reduction were considered responders to PDT-V (Fig. 1). When one or more of these signs of recovery were absent at the post-PDT-V examination, the patient was labeled as a nonresponder to PDT-V (Fig. 2). Both responders and nonresponders underwent re-treatments when needed, in accordance with the international guidelines for PDT-V application (TAP/VIP protocol).3

Genomic DNA was isolated from the peripheral blood by standard phenol-chloroform extraction and ethanol precipitation. Samples were polymerase chain reaction (PCR) genotyped for FVL-G1691A, FII-G20210A, FXIIIA-G185T, MTRR-A66G, MS-A2756G, and MTHFR-C677T gene variants, according to our previous reports.31–33 The expected allele frequencies in the whole group of investigated cases were checked by the Hardy-Weinberg equilibrium test for those SNPs showing a rate < 5% and compared with a cluster of normal subjects. The control subjects were matched for sex, age, and ethnicity with the case group.

Odds ratios (ORs) and 95% CIs were used to estimate the probability of having a satisfactory or unsatisfactory response to PDT-V.
respectively, in responder and nonresponder patients. Adjusted ORs for single or combined comparisons were calculated with logistic regression models, controlled for sex and age. Univariate and multivariate analyses were performed to determine which variables were predictive of PDT-V responder, using responder/nonresponder as the dependent binary variable. In these regression models, the putative predictors were included according to the clinical plausibility of their possible influence on the dependent variable. The following parameters were examined as PDT-V predictors: patient’s age, pre-PDT-V BCVA, pre-PDT-V CNV area, FVL-G1691A GA/AA, FII-G20210A GA/AA, FXIIIA-G185T GT/TT, MTRR-A66G AG/GG, MS-A2756G AG/GG, and MTHFR-C677T CT/TT. Those putative predictors that did not significantly contribute to the univariate logistic regression were ruled out from the final multivariate selected one (exclusion threshold, \( P < 0.05 \)).

### Table 1. Inclusion and Exclusion Criteria

**Inclusion criteria**
- Patient’s age > 65 years
- Diagnosis of AMD
- Best-corrected visual acuity better than 20/200 (Snellen equivalent)
- FA/ICGA diagnosis of occult with no classic CNV secondary to AMD
- CNV under the geometric center of the foveal avascular zone (subfoveal)
- Evidence of recent CNV progression
- Greatest diameter of entire CNV ≤ 4 MPS-DAs (equivalent to 10.16 mm² on the retina)

**Exclusion criteria**
- History of any other CNV treatment before PDT
- Presence of any other possible cause of CNV, such as degenerative myopia, angiod streaks, chorioretinal inflammatory diseases, hereditary retinal disorders, presumed ocular histoplasmosis syndrome, and/or severe ocular trauma
- Intraocular surgery and any ocular laser-treatment during the 6 months before or the 3 months after PDT-V
- Presence of any significant side effect, condition and/or event influencing PDT-V outcome
- Active or chronic systemic diseases (such as porphyria, diabetes mellitus, hepatopathies, metabolic, cardiovascular, and hematological disorders), as well as assumption of any medication, known to affect the hemostatic balance
- Protein intake, during breakfast or lunch, occurred 12 hours before PDT-V
- Lack of consensus about the definition of responder and non-responder to PDT-V

### RESULTS

Demographic and ophthalmic characteristics of the study population are summarized in Table 2. A single photodynamic treatment was sufficient in 16 of the 38 responders. On the other hand, after 3 months from the first PDT-V, re-treatment was necessary in all the other 68 (80.9%) enrolled subjects, including nonresponders (46 cases) and responders with residual signs of CNV activity (22 cases). This rate of application of the second PDT-V resembles the datum already observed during the VIP study (78.7%), which, however, also included 52 patients with classic CNV.\(^{15}\)

Genotype frequencies in the total study cluster, as well as in responders and nonresponders to PDT-V are reported in Table 3. Both FVL-G1691A and FII-G20210A showed an allele frequency <5%. In the investigated case group, no significant deviations from Hardy-Weinberg equilibrium (all \( P \approx 0.944 \)) and from genotype distribution of a healthy control population were observed for these SNPs. In detail: (1) in the FVL-G1691A cases (\( n = 84 \)), \( GG = 79, AG = 5, \) and \( AA = 0 \) versus the control group (\( n = 100 \)), \( GG = 97, GA = 3, \) and \( AA = 0 \); (2) in the FII-G20210A cases (\( n = 84 \)), \( GG = 78, AG = 6, \) and \( AA = 0 \) versus the control group (\( n = 100 \)), \( GG = 98, GA = 2, \) and \( AA = 0 \). Genotype distributions of FVL-G1691A and FII-G20210A detected within our control cluster were in accordance with those previously reported in Caucasians.\(^{29,30,41}\) Since both FVL 1691 GA/AA and FII 20210A GA/AA result in a well-known procoagulant predisposition in Caucasian subjects\(^{52–54}\) and are not present as frequently as the other examined SNPs, these genetic variants were also collectively analyzed (FVL 1691 GA/AA+FII 20210A GA/AA) owing to the absence of concomitant-carrier cases.

The ORs, adjusted by univariate logistic regression for the probability estimation of clinical efficacy (responders) or inefficacy (nonresponders) of PDT-V, are shown in Table 4. When each phenotypic or genotypic factor was examined on a univariate basis as putative PDT-V predictor, FVL-G1691A+FIIG20210A A carriers were more frequent within the responders, whereas FXIIIA-G185T T carriers were more commonly represented within the nonresponder group. In particular, FVLG1691A GA/AA+FII-G20210A A carriers were more frequent within the responders, whereas FXIIIA-G185T T carriers were more commonly represented within the nonresponder group. All the other predictive factors considered did not significantly modify the short-term CNV responsiveness to PDT-V application (Table 4). On selected multivariate analysis, including predictors with a univariate \( P \leq 0.10 \), only the FXIIIA-G185T GT/TT covariate still displayed influence on the PDT-V clinical outcome (\( OR = 0.29 \) [GT or TT versus GG], \( 95\% CI: 0.11–0.77; P < 0.05 \); Table 5).

### DISCUSSION

A heterogeneous variety of inherited or acquired clotting abnormalities are related to unbalanced hemostasis.\(^{29–38}\) Once
the thrombocoagulative process starts, whether physiologically or therapeutically triggered, both anticoagulative and fibrinolytic pathways are involved in modulating thrombosis in the ill-treated area. During PDT-V, the therapeutic photothermolysis is mainly due to a preferential photosensitizer binding to neovascular endothelium in comparison with that of normal macular vessels. The intravenously injected verteporfin couples with plasma low density lipoproteins (LDL) to form a complex, which is predominantly taken up into CNV endothelial cells via endocytosis, owing to an overexpression of LDL receptors in this neovascular lesion. The photodynamic damage to the CNV endothelium is activated by the oxidative action of numerous reactive oxygen species (ROS), acting as triggering agents for the hemodynamic stasis within the target neovascularization. In fact, ROS-related exposure of the vascular basement membrane initiates adhesion, degranulation and aggregation of the platelets, with consequent release of vasoactive mediators (i.e., thromboxane A2, histamine, prostaglandins, and/or tumor necrosis factor-α). These molecules elicit amplification of platelet activation, thrombosis, vasoconstriction, and increased vascular permeability, which synergistically cause blood hypoperfusion, hypoxia, and shutdown of the neovascular complex. This mechanism of action points out that three phases are reliably involved in determining the variable CNV responsiveness to standardized PDT-V: (1) the triggering of photochemical damage at the level of the neovascular complex; (2) the extent of photothermocoagulative occlusion within the neovascular complex; and (3) the persistence of CNV hemodynamic closure after verteporfin therapy. These distinctive events are consistently modifiable by the different genetic thrombophilic or antithrombophilic backgrounds of each individual. Recently, in Caucasian patients with classic or predominantly classic CNV secondary to AMD, Parmeggiani et al. documented the presence of significant predictive associations among diverse levels of PDT-V effectiveness and peculiar coagulation-balance SNPs: (1) the carriers of thrombophilic gene variants, directly predisposing to thrombosis through a higher thrombin generation (i.e., FVL-G1691A and FII-G20210A) or indirectly affecting thrombocoagulative functionality via hyperhomocysteinemic activation of endothelial cells and platelets (i.e., MTHFR-C677T), were characterized by a greater possibility of showing a benefit after PDT-V; (2) the PDT-V nonresponders were clearly overrepresented within the carriers of the FXIIIa-B allele, which induces an antithrombophilic diathesis that reduces the fibrin-clot stability. In the present study cluster, treated with PDT-V for occult CNV with no classic component, the same methodological approach was used to investigate these pharmacogenetic predictors, but the results just partially confirm those in the prior study. In fact, considering both classic and occult CNVs, FV-1691A results just partially confirm those in the prior study. In fact, considering both classic and occult CNVs, FV-1691A mon SNPs G1691A of the FV gene and G20210A of the FII gene were used to investigate these pharmacogenetic predictors, but the results just partially confirm those in the prior study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>NS</td>
<td>NR</td>
</tr>
<tr>
<td>Pre-PDT-V BCVA</td>
<td>NS</td>
<td>NR</td>
</tr>
<tr>
<td>Pre-PDT-V CNV area</td>
<td>NS</td>
<td>NR</td>
</tr>
<tr>
<td>FVL-G1691A (GA or AA)</td>
<td>NS</td>
<td>NR</td>
</tr>
<tr>
<td>FII-G20210A (GA or AA)</td>
<td>NS</td>
<td>NR</td>
</tr>
<tr>
<td>FVL-G1691A + FII-G20210A (GA or AA)</td>
<td>0.07 (NS)</td>
<td>3.8 (0.94–15.6)</td>
</tr>
<tr>
<td>FXIIIA-G185T (GT or TT)</td>
<td>&lt;0.01</td>
<td>0.28 (0.11–0.75)</td>
</tr>
<tr>
<td>MTHFR-C677T (CT or TT)</td>
<td>NS</td>
<td>NR</td>
</tr>
<tr>
<td>MS-A2756G (AG or GG)</td>
<td>NS</td>
<td>NR</td>
</tr>
<tr>
<td>MTRR-A66G (AG or GG)</td>
<td>NS</td>
<td>NR</td>
</tr>
</tbody>
</table>

OR, Odds ratio; CI, confidence interval; NS, not significant; NR, not relevant; other abbreviations as in Table 3.

### Summary of the Multivariate Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVL-G1691A + FII-G20210A (GA or AA)</td>
<td>NS</td>
<td>NR</td>
</tr>
<tr>
<td>FXIIIA-G185T (GT or TT)</td>
<td>&lt;0.05</td>
<td>0.29 (0.11–0.77)</td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 3 and 4.
availability in plasma.\textsuperscript{32–35} FV is a cofactor enzyme with pivotal roles in hemostatic equilibrium, especially stimulating the inactivation of factor VIIIa by activated protein C. In FV-1691A carriers, this anticoagulant function is altered with a consequent increased thrombin generation causing a prothrombotic state.\textsuperscript{30,33} Prothrombin is the central component of the coagulation cascade that, in its active form thrombin, regulates both pro- and anticoagulant processes. In FII-20210A carriers the elevation of prothrombin expression is due to functional abnormalities in its mRNA metabolism, which predisposes to thrombosis by affecting a tightly balanced architecture of non-canonical \( 3^\prime \) end formation signals.\textsuperscript{30,34} Consistently, as a consequence of their individual thrombophilic predisposition, our heterozygous A allele carriers of FV 1691 or FII 20210 gene appeared by be characterized by an higher possibility of receiving a clinical benefit from PDT-V, owing to a greater magnitude of CNV photothrombosis. This remarkable statistical trend supports the pharmacogenetic suitability of the study postulations, even if, in selected multivariate analysis, the FVL-G1691A GA/AA+FII-G20210A GA/AA covariate did not reach a significant rank, probably because of its minor frequencies with respect to the other included SNPs.

**Hyperfibrinolytic SNPs and Post-PDT-V Hemodynamic Recanalization in Occult CNV**

The three-dimensional analyses of FA/ICGA angiograms after PDT-V disclose several aspects about the “dark spot,” a typical retinocochorial circular hypofluorescence corresponding to the laser-light-exposed area. During the first hours after PDT-V, this angiographic pattern is just partially due to the photothromboses of CNV and collateral choroid, which are also associated with a massive fluid extravasation. One week later, the slow regression of exudation displays the whole extent of the post-PDT-V occlusive effects.\textsuperscript{21} However, this phase of blood nonperfusion is individually variable and, at 7-day check after PDT-V, the angiographic findings show that the CNV vascular net is still apparent in approximately half of the treated patients.\textsuperscript{20} The changeability in the post-PDT-V retinocochorial appearance may be associated with differences in fibrin structure, which influences the individual fibrinolytic rate.\textsuperscript{31,35} FXIII is the precursor of a transglutaminase that cross-links fibrin and, altering its network and properties, regulates fibrinolysis. The FXIII activation is modulated by FXIIIA-G185T polymorphism,\textsuperscript{35} a common genetic variation in Caucasians.\textsuperscript{31} Both the GT and TT genotypes cause modification in FXIII transglutaminase activity, which appears to be highly increased in homoygotes and exhibits an intermediate function in heterozygous carriers.\textsuperscript{31} In our study cluster, a reduced fibrin clot stability and persistence, followed by the early CNV recanalization, could explain the correlation between PDT-V’s inefficacy and the hyperfibrinolytic polymorphism of FXIII. Otherwise, the neoangiogenic properties ascribed to FXIII may in part account for this result. In fact, a more active FXIII molecule at the site of injury (i.e., in the FXIII T-carriers) could downgrade the benefit of PDT-V by contrasting the laser-induced ischemia. Our speculation is supported by the evidence of neovascularization development after FXIIIA injection in an experimental cornea model.\textsuperscript{44}

**Hyperhomozygostenic SNPs and Post-PDT-V Endothelial Response in Occult CNV**

The modalities by which PDT-V’s damage of the neovascular endothelium triggers the therapeutic CNV thrombosis\textsuperscript{37–45} resemble those occurring in the course of hyperhomocysteinemia due to folate-related gene variants.\textsuperscript{56,58} These SNPs cause enzymatic defects at different levels of the methionine-homocysteine pathway, inducing thrombophilic diathesis via hyperactivation of endothelial cells and platelets.\textsuperscript{56,58,60} Hyperhomozygostenic conditions lead to vascular changes as result of a ROS-related triggering,\textsuperscript{47–49} which initiates lipid peroxidation in endothelial cell membranes and in circulating LDL,\textsuperscript{57} causes overexpression of lectin-like oxidized LDL receptor-1,\textsuperscript{50,51} and enhances platelet activation.\textsuperscript{52} All these prothrombotic interactions among hyperhomocysteinemic and photodynamic oxidant effects, as well as our previous findings observed in AMD patients treated with PDT-V for classic CNV, strongly support the existence of a potential gene–environment interaction between PDT-V efficacy and thrombophilic SNPs affecting the homocysteine metabolism.\textsuperscript{17,36–39,45} However, in the present AMD cluster with occult CNV, no influence on PDT-V outcome is recordable considering as predictors those hyperhomozygostenic SNPs that convert vascular endothelium and natural anticoagulant pathway to a more prothrombotic phenotype. This discrepancy could provide the rationale for a pharmacogenetic interpretation of the clinical limits and unpredictability of standardized PDT-V application, especially considering the occult neovascular complex.\textsuperscript{3,7,15} In fact, the absence of any endothelium-related PDT-V predictors in occult CNV indirectly indicates that the vascular parietal pattern does not represent an ideal receptor target for the circulating verteporfin–LDL complex. Speculatively, the responsiveness to PDT-V of a large part of occult lesions seems to be scarcely determined by the photo-oxidative, LDL-mediated, endothelial triggering, probably because their endothelial cells do not possess those peculiar receptor properties characterizing the real aberrant neovascular ones. On the other hand, the higher odds of PDT-V benefit recorded in AMD patients with classic CNV and MTHFR-C677T polymorphism is attributable to an effectual photochemical activation during the first phases of CNV photothrombosis,\textsuperscript{59} consistently related to a more homogeneous overexpression of LDL receptors in the endothelium of classic CNVs.

In Caucasian patients with AMD with occult CNV, the present findings document the presence of gene–environment interactions between responsiveness to PDT-V and SNPs encoding enzymes relevant to the coagulation–fibrinolysis balance. Particularly, the post-PDT-V extent of CNV occlusion appears to be directly dependent on rare thrombophilic SNPs (i.e., FV-1691A+FII-20210A), whereas the post-PDT-V persistence of CNV shutdown appears to be inversely dependent on common hyperfibrinolytic genotypes (i.e., FXIIIA-185 GT or TT). Moreover, the retrospective assessment of hyperhomocysteinemic PDT-V predictors, carried out by comparing the results obtained in AMD study populations with classic\textsuperscript{59} or occult CNV, provides a possible intriguing explanation for the minor clinical responsiveness to PDT-V of the occult subfoveal lesions. In fact, the review of TAP/VIP data shows a remarkable difference in post-PDT-V severe vision loss between classic and occult CNVs, respectively: 33% versus 51% at 1 year, and 41% versus 55% at 2 years. The comprehensive appraisal of these controlled clinical findings and our predictive pharmacogenetic outcomes rationally support the hypothesis that standardized PDT-V is more effective in affecting the uncoagulable endothelial properties of classic CNV with respect to that occurring in occult CNV.\textsuperscript{7,15,39,46–55}

The clinical applicability of the present results mainly concerns the possibility of upgrading the PDT-V eligibility criteria in patients with AMD-related occult CNV, currently centered just on the monitoring of visual acuity and of changes in morphologic CNV composition.\textsuperscript{3,7,16,20} A preoperative genetic assessment of the individual thrombophilic background should provide support for a more rational selection of candidates for PDT-V.\textsuperscript{7,16,50} In particular, standardized PDT-V, in combination with anti-VEGF compounds, seems to be elective just for thrombophilic patients with FVL-G1691A and/or FII-G20210A
mutations, whereas no indication for PDT-V have been obtained in our carriers of hyperhomocysteinemic SNPs. Finally, among patients with hyperfibrinolytic FXIIIA-G185T polymorphism, anti-VEGF treatments alone are strongly suggested, both considering our post-PDT-V results, indicative of an early CNV recanalization related to insufficient fibrin clot persistence.51-55,59 and for the recently recognized outstanding proangiogenic properties of FXIII.57,58 This new exploratory attitude could address the question of proper dosimetry for an individually targeted PDT-V application in patients with AMD-related CNV, prospectively indicating a rationale to re-evaluate the suitability of previous notions regarding the optimized laser-light parameters.55-62 Further pharmacogenetic investigations with large controlled trials are warranted to outline the appropriate paradigm for improving the international guidelines of PDT-V.

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References


