Calculating the individual probability of successful ocriplasmin treatment in eyes with VMT syndrome: a multivariable prediction model from the EXPORT study

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bjophthalmol-2017-310874).

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DOG 2017115th DOG Congress28.9. – 1.10.2017Estrel Congress & Messe Center Berlin

Received 12 June 2017
Revised 7 September 2017
Accepted 7 October 2017
Published Online First 31 October 2017

ABSTRACT

Background/Aims To evaluate predictive factors for the treatment success of ocriplasmin and to use these factors to generate a multivariate model to calculate the individual probability of successful treatment.

Methods Data were collected in a retrospective, multicentre cohort study. Patients with vitreomacular traction (VMT) syndrome without a full-thickness macular hole were included if they received an intravitreal injection (IVI) of ocriplasmin. Five factors (age, gender, lens status, presence of epiretinal membrane (ERM) formation and horizontal diameter of VMT) were assessed on their association with VMT resolution. A multivariable logistic regression model was employed to further analyse these factors and calculate the individual probability of successful treatment.

Results 167 eyes of 167 patients were included. Univariate analysis revealed a significant correlation to VMT resolution for all analysed factors: age (years) (OR 0.9208; 95% CI 0.8845 to 0.9586; p<0.0001), gender (male) (OR 0.480; 95% CI 0.241 to 0.957; p=0.0371), lens status (phakic) (OR 2.042; 95% CI 1.054 to 3.958; p=0.0344), ERM formation (present) (OR 0.384; 95% CI 0.179 to 0.821; p=0.0136) and horizontal VMT diameter (µm) (OR 0.99812; 95% CI 0.99684 to 0.99941, p=0.0042). A significant multivariable logistic regression model was established with age and VMT diameter.

Conclusion Known predictive factors for VMT resolution after ocriplasmin IVI were confirmed in our study. We were able to combine them into a formula, ultimately allowing the calculation of an individual probability of treatment success with ocriplasmin in patients with VMT syndrome without FTHM.

INTRODUCTION

Vitreomacular traction (VMT) syndrome has been defined as an anomalous posterior vitreous detachment leading to foveal intraretinal structural changes without interruption of all retinal layers.[1] Ocriplasmin (Jetrea, ThromboGenics, Leuven, Belgium), a recombinant protein comprising the catalytic domain of human plasmin, was approved by the US Food and Drug Administration in October 2012[2] and by the European Medicines Agency in March 2013[3] for the treatment of vision-disturbing VMT with or without a full-thickness macular hole (FTMH). The therapeutic principle underlying ocriplasmin is 'enzymatic vitreolysis', which has been shown to significantly promote posterior vitreous detachment.[4]

In the registration trials (TG-MV-006 and TG-MV-007), a successful treatment—defined as the VMT resolution within 1 month following a single intravitreal injection (IVI) of 125 µg ocriplasmin—was observed in 26.5% of eyes treated.[4] Further analysis revealed predictive factors influencing therapeutic success. Younger individuals (<65 years of age), females and phakic patients had higher probabilities of VMT resolution.[5–7] With reference to the vitreoretinal interface architecture, it was demonstrated that eyes with a focal VMT diameter <1500 µm and without an epiretinal membrane (ERM) formation were favourable candidates for ocriplasmin treatment.[5–7]

It was interesting that among the published case series of ocriplasmin treatment for VMT syndrome, success rates varied significantly. Success ranged from 26.5% of the registration trials[4] up to 71% in a retrospective case series.[8] This marked difference was probably an effect of varying and individually changing criteria used for treatment selection.[9] The purpose of this study was thus to improve treatment selection through establishing a formula based on objective parameters. In a first step, known predictive factors were re-evaluated in data collected from a multicentre cohort trial. In a second step, a multivariate model was generated out of these factors—permitting the calculation of an individual probability of successful ocriplasmin treatment for patients with VMT syndrome for the first time. We believe that this information might be crucial for patients and physicians seeking a personalised best treatment option in a shared decision-making process pro or contra enzymatic vitreolysis.

METHODS

Our analysis was designed as a retrospective, multicentre cohort study based on the evaluation of

To cite: Paul C, Heun C, Müller H-H, *et al*. *Br J Ophthalmol* 2018;**102**:1092–1097.

patient charts and optical coherence tomography (OCT) scans. Patients were recruited at 11 medical centres: Berlin (DE), Bonn (DE), Cologne (DE), Düsseldorf (DE), Feldkirch (AT), Göttingen (DE), Heidelberg (DE), Munich (DE), Münster (DE) and Sulzbach (DE) as part of the EXPORT study.[10] They were included in this study if they fulfilled the following criteria:

a. They were diagnosed with a symptomatic VMT (defined as a disturbance of visual acuity in combination with a typical attachment of the posterior vitreous cortex (PVC) to the inner limiting membrane (ILM) and deformation of the common foveal contour accompanied by intraretinal cysts) without a FTMH.[1]
b. They received an intravitreal ocriplasmin therapy for VMT resolution.
c. A spectral domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) was performed within 2 days prior to the injection (to avoid false inclusion of spontaneous VMT resolution).
d. A follow-up OCT with the same device was conducted 28±5 days after injection (to assess therapeutic success defined as a complete cleavage of the PVC from the ILM in the scanned OCT frame—in accordance with the MIVI trials[4]).

Exclusion criteria were the diagnosis of VMT when associated with an FTMH, any other OCT machine used than the Spectralis device, no OCT performed either within 2 days prior to or 28 days after the injection or any other vitreoretinal pathology except ERM formation (eg, exudative age-related macular degeneration, diabetic macular oedema). All OCT examinations, including pretreatment and post-treatment, were performed through dilated pupils and analysed by two independent graders. Inclusion was within the time frame from July 2013 (first pretreatment OCT) to July 2015.

The focus of the statistical analysis was the development of logistic regression models for prediction of VMT resolution on the basis of the already described factors using the 'Statistical Analysis System' (SAS, V.9.2; SAS Institute, Cary, North Carolina, USA) and R (V.3.4.0, open source) software packages. First, univariate regression analysis was conducted to verify the association of the so-far described predictors. Next, multivariable logistic regression models were evaluated using a stepwise selection procedure and a score criterion-based approach. Variables were added if there was a significant additional effect for discrimination based on a level of the p value and the 'Akaike information criterion'. In addition to p values for influence as predictors, ORs were calculated to measure the strength of influence. ORs are provided as estimates, each with a 95% CI. In the two described multivariable logistic regression models, the intercept is provided in addition. Thus, the probability of a VMT resolution can be calculated for individual patients (either by the given formulas or by the supported JavaScript calculator (online supplementary file 1: 'ProbabilityCalculator.html'). To evaluate the multivariate models, individual probability of success was calculated for every patient. Patients with similar predicted success rates were grouped (20% intervals) and average de facto success rates were calculated for these groups. For cross-validation, a 'leave-one-out' procedure was adopted.

RESULTS

A total of 167 consecutive eyes of 167 patients were enrolled in our analysis. Of those, 49 (29.3%) were men and 118 (70.7%) were women. The mean age was 72.7±8.9 years (±SD). One hundred and eleven (66.5%) eyes were phakic and 56 (33.5%) were pseudophakic. ERM formation was present in 40 patients (24.0%). The horizontal VMT diameter was 467±418 µm (range: 50–2739 µm). Ocriplasmin therapy was successful in 79 cases (47.3%) and failed in 88 cases (52.7%).

The univariate regression analysis findings with the predictors analysed (gender, age, lens status, ERM formation, horizontal VMT diameter) and the mean values of these factors in each group (therapy success or failure) are found in table 1. All analysed factors correlated significantly to therapeutic success with the lowest p values observed for age and VMT diameter. Younger age and smaller diameter were correlated to VMT resolution. For the dichotomous parameters, a positive correlation to treatment success was found with female gender, phakic eyes and the absence of formation of ERM.

A correlation analysis was performed in between all factors. There was an association of age to lens status with older patients more likely to be pseudophakic. In addition, older patients more likely presented a larger VMT diameter (r=0.275) (details are given in online supplementary figure 1).

Multivariable logistic regression models were generated using a stepwise selection process. Linear modelling was used for all parameters except VMT diameter. For VMT diameter, logarithmic modelling exhibited a more even distribution and better correlation to treatment success versus linear modelling (data not shown). In a system with one variable, VMT diameter was the best parameter (χ^2 score: 18.88). In a system with two, VMT diameter and age (χ^2score: 28.97) were the best; in a system with three: VMT diameter, age and gender (χ^2 score: 31.04) were the best; in a system with four: VMT diameter, age, gender and ERM formation (χ^2 score: 32.11) were the best. A system with five parameters (with all factors that includes lens status) the χ^2 score was 32.98. The two-factor system (model A: age and VMT diameter) was statistically significant for both factors, while the three-factor system (model B: age, VMT diameter and gender) failed significance for gender (p=0.1437) with age and VMT diameter being significant (table 2). All four-factor and the five-factor systems failed significance (data not shown).

Table 1 Univariate regression analysis results of the analysed variables

Variable	VMT resolution	VMT persistence	OR (95% CI)	p Value
Gender, male	17 (21.5%)	32 (36.3%)	0.480 (0.241 to 0.957)	0.0371
Age, years	69.6 (±9.1)	75.5 (±7.9)	0.9208 (0.8845 to 0.9586)	<0.0001
Phakic	59 (74.7%)	52 (59.1%)	2.042 (1.054 to 3.958)	0.0344
ERM formation	12 (15.2%)	28 (31.8%)	0.384 (0.179 to 0.821)	0.0136
Diameter, µm	358.3 (±351.9)	565.2 (±449.4)	0.99812 (0.99684 to 0.99941)	0.0042

Displayed are either the mean value with SD for linear parameters (age, vitreomacular traction (VMT) diameter) or number and percentage for binary parameters (gender, lens status, epiretinal membrane (ERM) formation) with respect to the treatment success (VMT resolution) or treatment failure (VMT persistence) groups. Furthermore, the corresponding OR with a 95% CI per one unit difference for quantitative/continuous parameter, respectively, presence versus absence of the listed results for the binary parameters (eg, man vs woman) and the p value (p) for the difference in odds for/of VMT resolution are shown.

Table 2 Multivariate logistic regression analyses for successful vitreomacular traction (VMT) resolution: included variables (two for model A and three for model B) are depicted in the column 'variable' with respective ORs and p values in columns

Variable	Model A (two variables) OR (CI) p Value	Model B (three variables) OR (CI) p Value
Intercept	10.5133	10.4523
ln (Horizontal VMT diameter, µm)	0.38331 (0.218 to 0.674) 0.0009	0.37449, (0.212 to 0.662) 0.0007
Age, years	0.93379 (0.895 to 0.974) 0.0013	0.93857 (0.900 to 0.979) 0.0034
Gender, male	–	0.55289 (0.260 to 1.175) 0.1233

To evaluate the constituted multivariate models, the probability of successful treatment was calculated for each patient using models A and B according to the following formulas:

$$Odds_B = exp(intercept) * OR_{age}^{years} * OR_{diameter}^{\ln(\mu m)} * OR_{gender}^{1\upsilon 0}$$

$$Odds_B = exp(intercept) * OR_{age}^{years} * OR_{diameter}^{\ln(\mu m)} * OR_{gender}^{1\upsilon 0}$$

The odds values were then converted to probabilities via:

$$\text{Probability}\,[\%] = \text{Odds}/(\text{Odds} + 1).$$

As an example, the probability of a 52-year-old woman with a focal VMT of 297 µm was 81.63% (following formula A) or 82.68% (following formula B):

$$\text{Odds}_{\text{A, Patient 1}} = e^{10.5133} * 0.93379^{52} * 0.38331^{\ln(297)} = 4.44297$$
$$\Rightarrow \text{Probability}_{\text{A, Patient 1}} = \frac{4.44297}{(4.44297+1)} = 81.63\%$$

$$\text{Odds}_{\text{B, Patient 1}} = e^{10.4523} * 0.93857^{52} * 0.37449^{\ln(297)}$$
$$0.55289^0 = 4.77448 \Rightarrow \text{Probability}_{\text{B, Patient 1}} = \frac{4.77448}{(4.77448+1)} = 82.68\%$$

As a second example, the probability of a 93-year-old man with a focal VMT of 1276 µm was only 6.21% (following formula A) or 4.48% (following formula B):

$$\text{Odds}_{\text{A, Patient 2}} = e^{10.5133} * 0.93379^{93} * 0.38331^{\ln(1276)} = 0.06619$$
$$\Rightarrow \text{Probability}_{\text{A, Patient 2}} = \frac{0.06619}{(0.06619+1)} = 6.21\%$$

$$\text{Odds}_{\text{B, Patient 2}} = e^{10.4523} * 0.93857^{93} * 0.37449^{\ln(1276)}$$
$$0.55289^1 = 0.04687 \Rightarrow \text{Probability}_{\text{B, Patient 2}} = \frac{0.04687}{(0.04467+1)} = 4.48\%$$

To visualise the results from model A, the probability of successful treatment with ocriplasmin was plotted based on dependence of age and horizontal VMT diameter (figure 1).

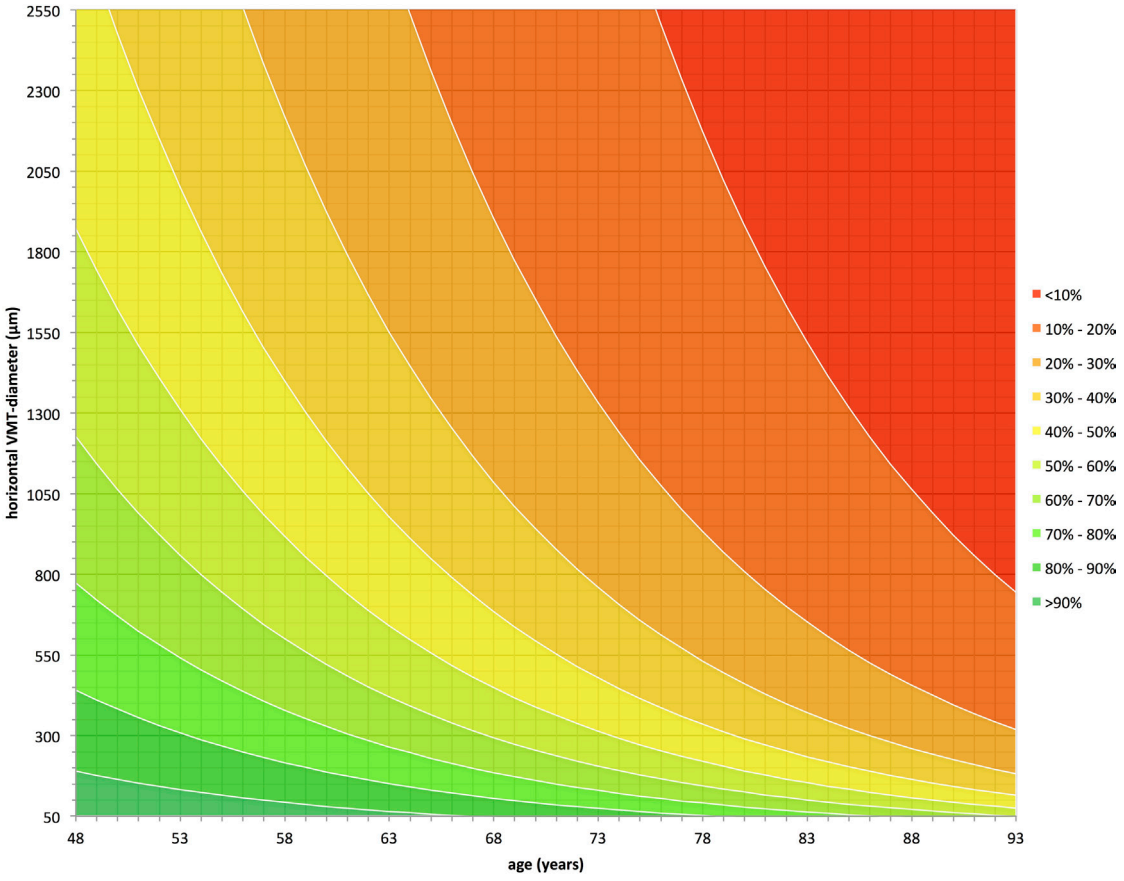

Figure 1 Two-dimensional plot of the probability of successful treatment with ocriplasmin: model A was used to calculate the probability of successful treatment (grouped in 10% intervals; red to green colours) with a dependence on age (x-axis) and horizontal vitreomacular traction (VMT) diameter (y-axis). The x-scale and y-scale are based on the analysed patient cohort (with a range of ages from 48 to 93 years and a range of horizontal VMT diameters from 50 to 2563 µm).

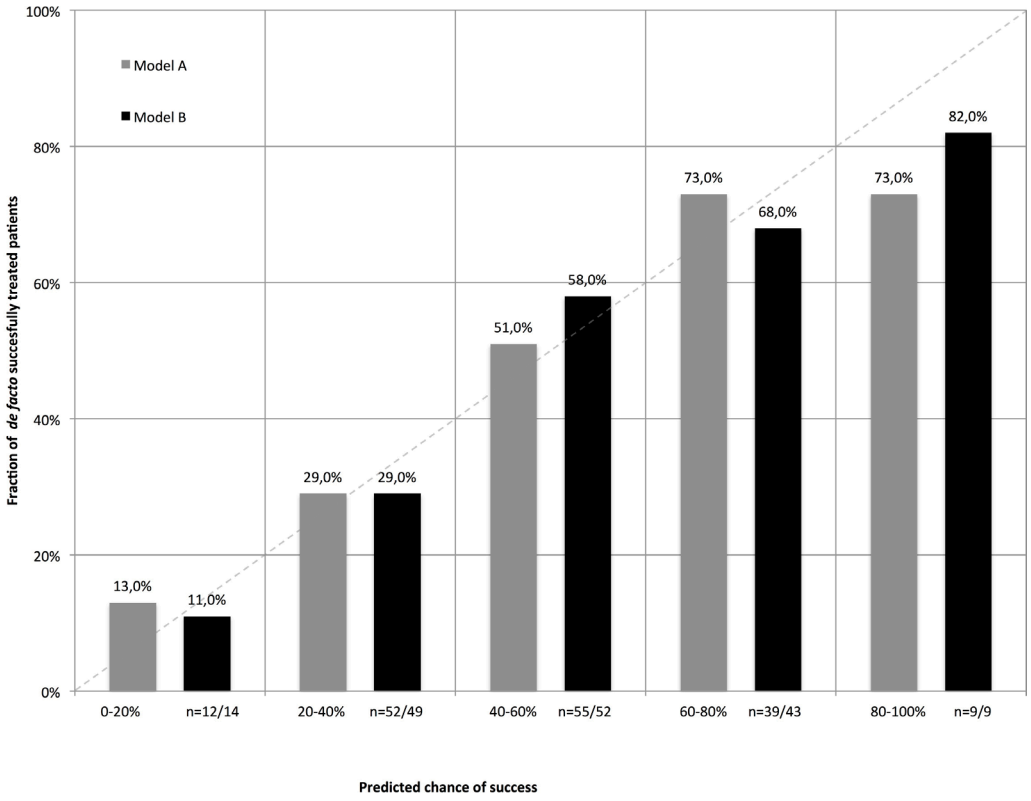

Figure 2 Evaluation of multivariate models A and B—correlation of predicted probability of success to the de facto success rate: the individual probability of ocriplasmin treatment success was calculated for every patient as described in table 2. Patients were then grouped by their probability of success (20% intervals, X-axis) and correlated to the de facto success rate within this group (Y-axis, proportion of successfully treated patients vs all treated patients in this group). Calculations were carried out with model A (age, vitreomacular traction (VMT) diameter; presented in grey) and model B (age, VMT diameter, gender; presented in black). Number (n) of patients per interval is given for models A and B.

To evaluate both models, patients with similar probabilities were grouped in 20% intervals. In those interval groups, average de facto success rates were calculated. Predicted and de facto success rates are plotted in figure 2. Notably, the highest individual calculated success rate was 95.5% and the lowest individual rate was 6.7%.

To further evaluate and cross-validate the two-factor model A, a receiver-operating characteristic (ROC) curve was plotted (figure 3, black). A 'leave-one-out cross-validation' (LOOCV) procedure was employed to again plot the ROC curve (figure 3, grey). While both ROC curves shared a similar profile, the calculated area under the curve (AUC) was slightly reduced in the 'model A LOOCV ROC' (AUC=0.7214) in comparison to the 'model A ROC' (AUC=0.7363).

DISCUSSION

In patients with symptomatic VMT syndrome, there are currently three main therapeutic options that exist: a 'watchful-waiting' approach, a pars plana vitrectomy (ppV) or the 'enzymatic vitreolysis' induced by intravitreal ocriplasmin injection. The 'watchful-waiting' approach does not have any iatrogenic risks and VMT does resolve spontaneously in 32%–43% of cases.[11 12] However, this may take 266–617 days,[12] is only successful in every second to third patient and there is the risk of FTHM development. A ppV offers VMT resolution in virtually any patient. However, it is the most invasive option with considerable risks, including postoperative retinal detachment and cataract induction.[13] Ocriplasmin injection is, on the one hand, less risky compared with ppV and adverse events seem to be rare.[14 15] On the other hand, success rates are considerably lower, ranging from 26.5% to 71% of eyes treated.[4 5 8 16–21] As is already known, the therapeutic success rates of ocriplasmin are dependent of multiple factors, including age, gender, VMT diameter, ERM formation, existence of an FTMH and lens status.[5–7 22] Therefore, patient selection is challenging, yet crucial.[15]

The sample size of 167 eyes in our study was relatively large.[6 22] The overall success rate was 47.2% and comparable to previous publications with an average success rate of 46%.[6] We were able to confirm that the factors, age, gender, VMT diameter, ERM formation and lens status, had a statistically significant impact on therapeutic success.[4 5 7 16] The strongest association (derived by p value) with treatment success was determined for VMT diameter and age. The strength of the effect (derived by OR) was highest with the dichotomous variables, gender, ERM formation and lens status. It has to be taken in account, though, that for probability prediction, exponents for those factors are either 0 or 1, while, for example, VMT diameter, exponents range from 50 to 2739, explaining the strong influence on predicted probability of success even though its OR was 'only' 0.998 (compare to table 1). The calculated ORs in our study are similar to previous investigations (male gender: 0.480–0.422; phakic lens status: 2.04–3.02; ERM presence: 0.384–0.211, higher success rates in younger patients and smaller VMT diameter).[6]

In addition, the coexistence of an FTHM has been described to impact treatment success[4 5 7 16] as well as the absence of retinal comorbidities (eg, exsudative age-related macular degeneration

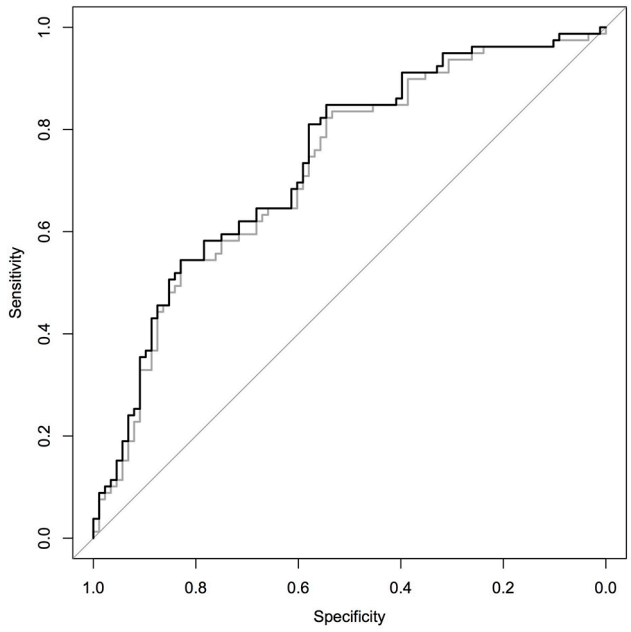

Figure 3 Receiver-operating characteristic (ROC) curve of model A and the ROC curve of the leave-one-out cross-validation (LOOCV) of model A. The sensitivity (y-axis) is plotted as a function of the specificity (x-axis). Black represents the 'model A ROC' and grey the overlaid 'model A LOOCV ROC'. The area under the curve is 0.7363 for the 'model A ROC' and 0.7214 for the 'model A LOOCV ROC'.

or diabetic retinopathy)[23] which was not analysed seeing that these patients were not included in this study. The duration of VMT, which might influence treatment success, was not assessed, either, as we did not have reliable pertinent data. Furthermore, not evaluated were specific angles in the vitreoretinal interface, which we recently described to have an effect on ocriplasmin treatment success.[24] OCT scan quality did not permit these examinations in all patients from this study. Affiliation to ethnic groups was not surveyed in our study. However, because of the distribution within German and Austrian societies, we assumed having included primarily Caucasians.

To our knowledge, we have undertaken the first attempt to calculate the individual probability of successful ocriplasmin treatment in patients with VMT syndrome based on a significant multivariate regression analysis. While many factors were already known, especially since the reanalysis of the MIVI trials,[7 25] combination of these factors was not performed and outcome predictions were not calculated.

Multivariate regression models tend to be the more accurate the more independent factors they include. However, the number of patients needed to reach statistical significance increases exponentially with each added factor. This context is reflected in our data. While all factors were significant within the univariate regression analysis, only the two-factor multivariate regression analysis reached significance for both factors. All systems with more than two factors failed significance—most likely based on the limited number of 167 patients. Of note, the three-factor model (model B including VMT diameter, age and gender) predicted the treatment success slightly more precisely (figure 2) and failed significance only with one of the three factors. It seems an appealing model if one can collect data from a sufficient number of patients to reach significance. Adding lens status as a fourth factor improved prediction values rather minimally. It is debatable whether it is merely a surrogate to patient age, which it is highly correlated to, or an individual factor on its own. It was hypothesised that vitreomacular adhesion might be firmer in patients in which cataract surgery did not induce posterior vitreous detachment.[7] For eyes with ERM formation, it has been a consensus among most authors that treatment with ocriplasmin should not be performed. As this has been understood since the registration trials,[4] our study most likely suffers from a selection bias that included, most probably, only cases with minimal ERM formation. Those ERM formations found in our OCT readings had strongly negative impact on treatment success (OR 0.384), and we conclude that such patients should not be treated with ocriplasmin. Therefore, an implementation of this factor in our prediction model seems dispensable. The integration of recently reported angles of VMT as a predictive factor shows more promise—it appears to be independent of the other known factors.[24] Yet, such a four-factor system will necessitate an even larger patient cohort—a challenge for future research. When transferring the here described model to clinical practice one has to consider that data were collected in a retrospective study, with the risk of a selection bias. Also, a validation on separate patient cohort has not yet been undertaken. Therefore, the external validity of the model may not yet be judged.

As a conclusion to the reported findings, our future efforts will focus on the evaluation of the herein described models on an independent patient cohort and establishment of similar prediction models for the ppV or the watchful-waiting approach. In our opinion, the best decisions—in a shared decision-making process—are made when patients and physicians know the individual probability of success or failure of each treatment option available.

We believe the described two-factor prediction model to be of major clinical relevance. It might aid ophthalmologists in deciding individually in an evidence-based fashion for or against ocriplasmin treatment in eyes with VMT syndrome without FTMH.

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Contributors CP analysed and interpreted the data, wrote, proofed and revised the article. H-HM performed the statistical analysis. All the authors have contributed substantially to conception and design, acquisition of data and interpretation of data; revising it critically for important intellectual content and final approval of the version to be published.

Competing interests HH reports personal fees from Allergan, personal fees from Alcon, personal fees from Bayer, personal fees from Heidelberg Engineering, personal fees from Novartis, personal fees from Alimera, outside the submitted work; NF reports personal fees and non-financial support from Allergan, personal fees and non-financial support from Bayer, personal fees from Heidelberg Engineering, personal fees and non-financial support from Novartis, personal fees and non-financial support from Alimera, outside the submitted work; JW reports personal

fees from Allergan, personal fees from Bayer, personal fees from Novartis, personal fees from Alcon, outside the submitted work; HK reports personal fees from Abbott Medical Optics, personal fees from Alimera Sciences, personal fees from Alcon, personal fees from Allergan, personal fees from Carl Zeiss Meditec AG, personal fees from Dres. Schlegel + Schmidt, personal fees from Ellex, personal fees from Geuder, personal fees from Novartis, personal fees from Oculentis, personal fees from Oertli Instrumente AG, personal fees from Polytech Domilens, personal fees from Topcon Medical, outside the submitted work; SM reports personal fees from Bayer healthcare, personal fees from Novartis, outside the submitted work; MJK reports personal fees from Allergan, personal fees from Allimera, personal fees from Bayer, personal fees from Insight Instruments, personal fees from Novartis, outside the submitted work; SF reports personal fees from Roche, outside the submitted work; MMM reports personal fees from Allergan, personal fees from Bayer, personal fees from Novartis, personal fees from Heidelberg Engineering, personal fees from Alcon, personal fees from Zeiss, outside the submitted work; RGS reports personal fees from Allergan, personal fees from Novartis, outside the submitted work; SM has nothing to disclose. PC reports personal fees from Novartis, outside the submitted work; PS has nothing to disclose. AL reports personal fees from Alcon, personal fees from Bayer, outside the submitted work; TB reports personal fees from Alcon, personal fees from Novartis, personal fees from Alimera, personal fees from Bayer, personal fees from Heidelberg, outside the submitted work.

Provenance and peer review Not commissioned; externally peer reviewed.

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