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ORIGINAL RESEARCH

Anatomical and Functional Outcomes of Anti-VEGF Therapy in Pachychoroid Neovasculopathy

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Background: Evaluation of real-life effectiveness of anti-VEGF therapy in patients diagnosed with pachychoroid neovasculopathy (PNV).

Methods: This retrospective analysis included central serous chorioretinopathy (CSC) patients who developed PNV and underwent anti-VEGF treatment. Individuals with concomitant retinal diseases were excluded. Key measures included best-corrected visual acuity (BCVA), spectral domain optical coherence tomography (SD-OCT) features (intra-/subretinal fluid, central retinal thickness (CRT), and choroidal thickness (CT)), and potential risk factors such as age, sex, and corticosteroid intake, baseline neovascularization area in fluorescein angiography and in OCT-angiography, and time from PNV diagnosis to treatment initiation.

Results: The study included 40 eyes of 40 patients (24 males, 16 females), with a mean follow-up period of 38.23±19.73 months and a mean number of anti-VEGF injections of 27.47±16.73. BCVA, CRT and CT improved significantly at the final visit compared to baseline (BCVA p=0.019, CRT p<0.001, CT p<0.001). 85% of eyes achieved a "completely dry" status on SD-OCT after a mean of 10.94±11.22 months and a mean of 8.88±9.17 injections. However, 82.4% of these eyes had a recurrence after a mean 3.32±4.82 months. There was no significant association of the evaluated risk factors with the treatment response. At the end of the observation period, there was no significant difference in BCVA between the "completely dry" group and the non-responders (p=0.765).

Conclusion: A majority of PNV patients exhibit anatomical and functional improvement following anti-VEGF therapy. However, the high rate of recurrences suggests a need for long-term treatment.

Keywords: pachychoroid neovasculopathy, chronical central serous chorioretinopathy, anti-VEGF therapy

Introduction

Pachychoroidal neovasculopathy (PNV) is a novel term to describe macular neovascularization (MNV) in association with abnormally thickened and altered choroidal vessels. PNV is part of the pachychoroid spectrum, which also includes pachychoroid pigment epitheliopathy, central serous chorioretinopathy (CSC) and pachychoroid aneurysmal type 1 MNV (PAT1), formerly known as polypoidal choroidal vasculopathy.[1,2] There is a pathophysiological overlap between these diseases, and in this continuum PNV is discussed as a secondary complication in the context of chronic CSC or other pachychoroidal diseases.

Without intervention, PNV may result in a substantial decline in central vision. Recent research has demonstrated the efficacy of anti-VEGF in addressing PNV.[3–10] In addition, photodynamic therapy (PDT) has been evaluated as a potential monotherapy and as an adjunct to anti-VEGF therapy.[3,11–16]

The aim of this study was to examine the long-time effectiveness of anti-VEGF therapy in patients with PNV. Furthermore, we aimed to identify possible risk and protective factors for good anatomical and functional response.

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Materials and Methods

Patients

All available patients' charts with a diagnosis of macular neovascularization (MNV) secondary to CSC who received anti-VEGF treatment between January 2015 and October 2023 at the Department of Ophthalmology, University Clinic of Cologne, were retrospectively reviewed. Only therapy-naïve patients without prior anti-VEGF treatment and with available multimodal imaging were included (Figure 1). Only one eye per patient was included. The diagnosis of PNV was documented by spectral domain optical coherence tomography (SD-OCT), OCT angiography (OCT-A), fundus autofluorescence (FAF), fluorescein angiography (FA), and indocyanine green angiography (ICGA). Patients with follow up less than 6 months and patients with signs of concomitant retinal diseases (myopia >6dpt, age-related macular degeneration, macular dystrophy, diabetic retinopathy, MNV due to other cause like trauma or tumor) were excluded.

Demographic information and medical history (corticosteroid intake, psychological stress, PDT treatment before and/or after diagnosis of PNV) were examined by reviewing patient records. Best-corrected visual acuity (BCVA) in logarithm of the minimum angle of resolution (logMAR) was obtained at baseline and at the end of the study for all

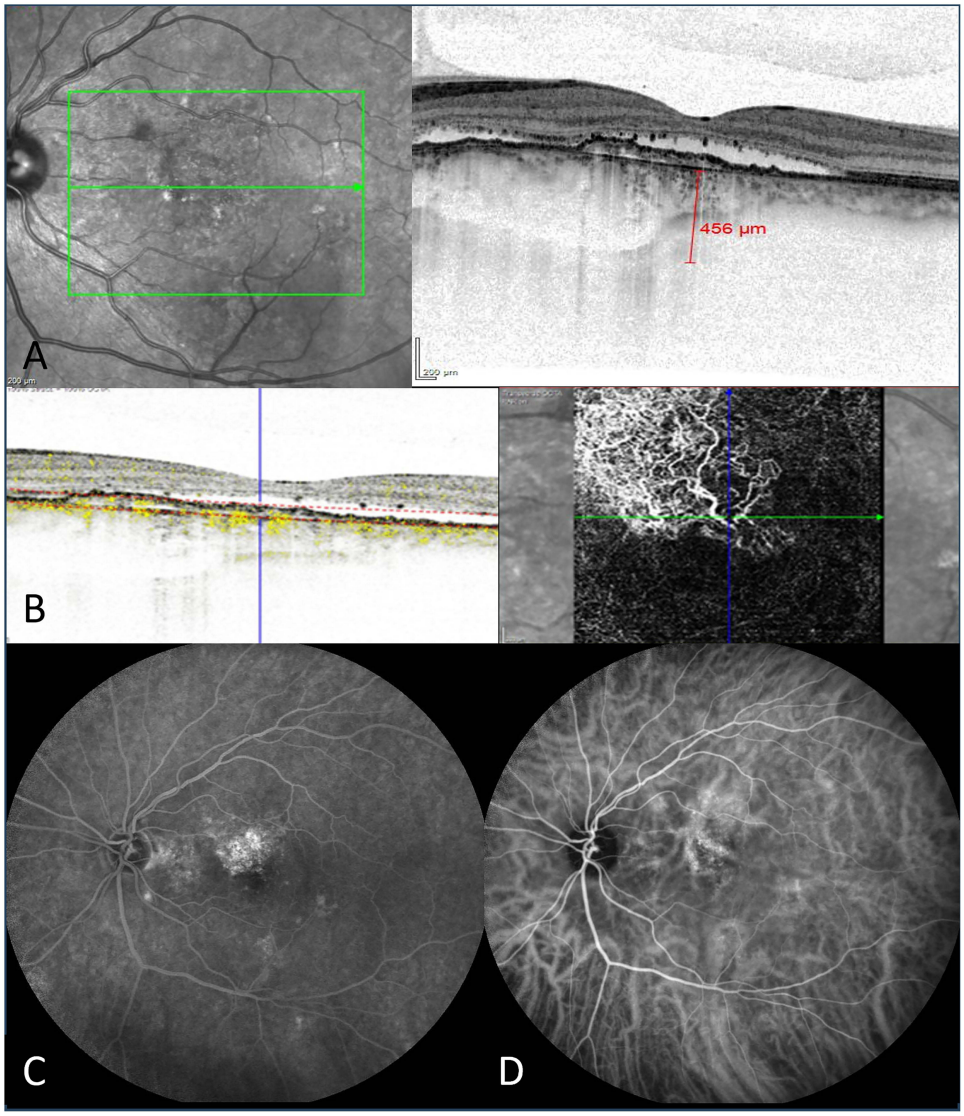

Figure 1 Multimodal imaging. (**A**) Optical coherence tomography (OCT) with flat irregular hyperreflective retinal pigment epithelium (RPE), macular subretinal fluid and thickened subfoveal choroid (**B**) OCT-angiography with neovascularization membrane (**C**) Late leakage on fluorescein angiography corresponding to the flat irregular hyperreflective retinal pigment epithelium (**D**) Mid-phase indocyanine green angiography with thickened choroidal vessels.

eyes. The study was conducted in accordance with the tenets of the Declaration of Helsinki and the Medical Research Involving Human Subjects Act (WMO).

Diagnosis and Grading of PNV

All available images were reviewed for the diagnosis of CSC and MNV. Grading was performed on FA/ICGA (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany), OCT-A, FAF and SD-OCT (scan area 20° × 15° (5.9 × 4.4 mm), 37 B-scans, distance between B-scans 123 mm) by two independent graders (VS, LA). Any discrepancies between graders were resolved through open adjudication. Morphological features for the confirmation of CSC diagnosis included presence of macular subretinal fluid (SRF) on SD-OCT, alterations in the retinal pigment epithelium (RPE), focal or diffuse leaks/ hyperfluorescent areas on FA/ICG-A and thickened choroid. The presence of neovascularization was defined by a late leakage on FA, corresponding to a late staining area on ICGA and a flat irregular, hyperreflective RPE elevation on SD-OCT.[17]

Central retinal thickness (CRT), choroidal thickness (CT), presence of RPE atrophy or intraretinal cysts were graded on SD-OCT at baseline and at the final visit. (Figure 1) For all measurements, automated segmentation of Heidelberg Eye Explorer software was used, and all results were corrected manually. Hereby, CRT was measured from internal limiting membrane to Bruch´s membrane (BrM), CT was measured on a subfoveal centered SD-OCT image. Neovascularization area was manually graded on FA and on OCT-A at baseline visit. In OCT-A, the neovascularization area was identified after manual correction of the segmentation in the subretinal and sub-RPE spaces.

Patient Treatment

All included eyes underwent anti-VEGF treatment with either Bevacizumab, Ranibizumab or Aflibercept in the Department of Ophthalmology, University of Cologne. The following treatment regimens were assigned and decided upon within routine clinical practice: 1) One single anti-VEGF followed by injections as needed, 2) Pro re nata (PRN with upload: 3 consecutive monthly injections followed by injections as needed, 3) Modified Treat & extend (T&E): one single anti-VEGF followed by T&E. In general, patients who started therapy between 2015 and 2018 were mostly assigned to one single anti-VEGF followed by monthly OCT controls and injections as needed or to PRN. Patients who started treatment in 2018 or later were assigned directly to modified T&E (without upload). Therapy success was defined as complete SRF resolution ("completely dry"). Best-corrected visual acuity (BCVA) was obtained at each visit.

Statistical Analyses

Descriptive statistics were used to summarize the characteristics of all patients. Results were given as mean ± standard deviation (SD), median ± interquartile range (IQR) or number of eyes and percentage. Pearson's chi² test was used for categorical variables and *t*-test or Mann–Whitney *U*-Test for continuous variables depending on the distribution. Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corporation). P values <0.05 were considered as statistically significant.

Results

About, 97 patients' charts were retrospectively reviewed. In total, 40 eyes of 40 patients fulfilled the inclusion and none of the exclusion criteria. Fifty-seven eyes were excluded due to one of the following reasons: 1) prior anti-VEGF injections (N=13), 2) follow-up less than 6 months (N=7), 3) missing retinal imaging data for the confirmation of CSC and MNV (N=9), 4) concomitant retinal diseases (N=28).

The mean observation time was 38.23 months, during which a mean of 27.47 injections were administrated. The majority of eyes (N=30, 75%) had T&E regimen from the beginning of the treatment. Only three eyes received 3x monthly upload followed by PRN regimen: one case had a recurrence after discontinuation of the treatment and did not receive any further follow up, another case reached a completely dry status and did not receive any further follow up, the third case switched to T&E before reaching a completely dry status. Seven eyes received primary one single anti-VEGF followed by monthly OCT controls, in cases of disease activity another anti-VEGF was administrated. Over time, six of the seven patients were switched to T&E due to high disease activity. One case reached a completely dry status only after 2 injections (duration between the two injections 3 months) and did not receive any further follow up.

Table 1 Demographics

Total number of patients	40
Total observations time (mean±SD, months)	38.23 ± 19.73
Total number of anti-VEGF injections (mean±SD)	27.47 ± 16.73
Time from CSC to PNV diagnosis (mean±SD, years)	3.52 ± 6.03
Time from PNV diagnosis to treatment start (mean±SD, days)	25.08 ± 32.25
Sex (male (%))	24 (60)
Age (mean±SD, years)	59.07 ±10.40
BCVA at baseline logMar (mean±SD)	0.55 ± 0.32
BCVA at final visit logMar (mean±SD)	0.43 ± 0.34
CRT at baseline (mean±SD, µm)	348.83 ± 81.21
CT at baseline (mean±SD, µm)	280.00. ± 55.67
Completely dry status (yes (%))	34 (85)
Recurrence after completely dry status (yes (%))	28 (82)
History of PDT (%)	16 (40)
Pseudophakic (%)	5 (12.5)

Abbreviations: Anti-VEGF, anti-vascular endothelial growth factor; BCVA, Best corrected visual acuity; CRT, Central retinal thickness; CSC, Central serous chorioretinopathy; CT, Subfoveal Choroidal thickness; logMar, Logarithm of minimum angle of resolution; PDT, Photodynamic therapy; PNV, Pachychoroid neovasculopathy; SD, Standard deviation.

Seventeen eyes received bevacizumab as an initial drug, 23 received ranibizumab as an initial drug and none of the eyes received aflibercept from the start. Twenty eyes (50%) switched the treatment to another drug during the course of observation. In general, until the last visit, each eye received a mean of 27.48±16.72 SD injections (median 25.00, range 55, min 2-max 57): bevacizumab mean 4.5±6.36 (median 0.00, range 24, min 0-max 24); ranibizumab mean 11.28±11.53 (median 9.00, range 40, min 0-max 40); aflibercept mean 11.70±13.42 (median 7.50, range 45, min 0-max 45). Further baseline characteristics are shown in Table 1.

Anatomical and Functional Outcome

A positive effect of the treatment could be demonstrated in all eyes regarding anatomical features (presence of SRF, CRT, CT). The majority of eyes (85%) reached a completely dry status on the SD-OCT (85%) after a mean of 10.94±11.22 months and after mean of 8.88±9.17 injections. However, 82.4% of those eyes had a reactivation after a short period of time (within 3.32±4.82 months).

Both CRT and CT were significantly reduced after treatment with anti-VEGF at the final visit, compared with baseline (mean change CRT 90.73±81.96 µm, $p<0.001$, mean change CT 36.76±30.00 µm $p<0.001$), regardless of the current activity of the neovascularization at the final visit (n=16 with dry SD-OCT, n=24 with presence of SRF).

Additionally, a significant improvement of BCVA could be shown (mean change from baseline to final visit BCVA 0.12±0.30, p=0.019). There was no statistically significant correlation between visual outcome and age or outcome in the CRT parameters and age (Pearson test $p>0.05$). Interestingly, among the eyes which reached a dry status, there was a significant correlation between the baseline neovascularization area in OCT-A and time until reaching a dry status with smaller areas drying quicker (P=0.038). The baseline neovascularization area in fluorescein angiography showed a tendency regarding the velocity of reaching a dry status, but did not reach the threshold for statistical significance (P=0.057).

PDT Treatment

Sixteen of the examined eyes had a history of PDT treatment. About, 13 of those 16 eyes had at least one PDT treatment before developing PNV. The mean time between first PDT treatment and first intravitreal injection was 3.11±2.47 years. Only 5 eyes had PDT after diagnosis of PNV (2 of them had PDTs before and after PNV diagnosis, 3 had PDT treatment only after PNV diagnosis). Among these cases, 3 eyes successfully reached a dry status, and two eyes were complete non-responders.

The remaining 24 eyes (60%) were never treated with PDT. 95.8% (n=23) reached a completely dry status during the anti-VEGF treatment, so no adjunctive PDT treatment was necessary.

Almost all non-responders to anti-VEGF had at least one PDT treatment (5/6). One patient did not receive any PDT because that was the patient's preference.

Prognostic Factors for Complete SRF Resolution

None of the evaluated demographic characteristics such as age, sex, time to treatment after diagnosis or corticosteroid intake could show a significant impact on reaching a completely dry status on SD-OCT. Also, none of the evaluated morphological features reached statistical significance (Table 2). History of PDT was highly significant.

Table 2 Prognostic Factors for Reaching a Completely Dry Status

	At Least Once Completely Dry	**Never Dry**	**p-value**
Total number of eyes	34	6	
Age at baseline (mean±SD, years)	58.82 ± 10.82	60.50 ± 8.17	0.721*
Sex (male (%))	20 (58.8)	4 (66.7)	0.718†
Total observation time (mean±SD, months)	37.9 ± 20.46	40.0 ± 16.45	0.815*
Total number of injections (mean±SD)	26.62 ± 16.44	32.33 ± 19.13	0.447*
Time from CSC to PNV diagnosis (mean±SD, months)	42.94 ±76.95	36.00 ± 40.89	0.832*
Time from PNV diagnosis to treatment start (mean±SD, days)	22.74 ± 28.87	38.33 ± 48.60	0.476*
BCVA at baseline logMar (mean±SD)	0.56 ± 0.32	0.43 ± 0.29	0.358*
CRT at baseline (mean±SD, µm)	355.56 ± 84.88	310.67 ± 42.79	0.069*
CT at baseline (mean±SD, µm)	281.94 ± 54.08	269.00 ± 68.59	0.606*
Intraretinal cysts (%)	30 (88.2)	1 (16.7)	0.738†
RPE atrophy (%)	5 (14.7)	0 (0)	0.315†
Neovascularisation area in OCT-angiography (mm^2)	1.58 ± 1.27	0.16 ± 0.14	0.377*
Neovascularisation area in FA (mm^2)	3.10 ± 2.96	1.99 ± 1.41	0.137*
Psychological stress (%)	11 (32.4)	3 (50.0)	0.622†
Cortisone intake (%)	4 (11.8)	2 (33.3)	0.241†
History of PDT (%)	11 (32.4)	5 (83.3)	0.019†

Notes: *T-Test, †Pearson's chi² test.

Abbreviations: BCVA, Best corrected visual acuity; CRT, Central retinal thickness; CSC, Central serous chorioretinopathy; CT, Subfoveal choroidal thickness; FA, Fluorescein angiography; logMar, Logarithm of minimum angle of resolution; OCT, Optical coherence tomography; PDT, Photodynamic therapy; PNV, Pachychoroid neovasculopathy; RPE, Retinal pigment epithelium; SD, Standard deviation.

Discussion

In this retrospective study, we analyzed a long term treatment response of anti-VEGF therapy in cases diagnosed with PNV. The majority of eyes achieved complete resolution of SRF on SD-OCT, confirming the efficacy of anti-VEGF treatment in eyes with PNV demonstrated in previous studies (4–8, 20–22). Nevertheless, after a short period of time there was a recurrence of disease activity which required a continuation of the treatment.

PNV is considered as a new disease entity that can occur directly or can develop after a long-standing chronic CSC.[18–20] Most common treatment options for PNV include anti-VEGF injection or PDT, or a combination of both. Most of the previous studies documented significant anatomical and functional improvements following anti-VEGF injections in PNV patients.[3,8,10,21–23] Yet, a recent retrospective study revealed that a relatively low rate of 41% of patients experienced successful treatment outcomes (characterized by complete resolution of symptoms), over a five-year period and reported no significant visual improvement.[24] These observed discrepancies may be attributable to a number of factors, including the administration of only one anti-VEGF agent, patient compliance, treatment regimens (single injection, PRN or T&E) or disease recurrence. In our cohort, the anti-VEGF medication was switched in cases of non-response and most of the patients followed a T&E regime. A recent retrospective study with a small cohort over a 3-year period of treatment suggested a superior effect of aflibercept over bevacizumab und ranibizumab.[25] Several studies have reported a comparable treatment effect of anti-VEGF treatment in patients with PNV and neovascular age-related macular degeneration (nAMD), with some even showing a reduced needed number of injections in PNV. (4–8, 14) Hata et al showed a significantly lower VEGF concentration in patients with treatment-naïve PNV in comparison to patients with treatment-naïve nAMD, suggesting a different influence of VEGF in PNV patients.[26]

PDT is considered to be a successful potential treatment option for PNV cases as a monotherapy, with comparable results to monotherapy with anti-VEGF injections.[3,20,27] Further, the efficacy of PDT in combination with anti-VEGF therapy has been evaluated for pachychoroidal neovasculopathy with or without polyps in several studies, demonstrating regression of MNV activity and a reduction in choroidal permeability.[11,13,15,16,28] For instance, Lee et al showed a positive effect of adjunctive PDT treatment for patients with type 1 MNV and thickened choroid who were refractory to anti-VEGF monotherapy, with 85.7% of patients reaching a dry status.[29] There are also a few long-term reports confirming the effectiveness of a combination therapy.[25,30] In our cohort history of PDT showed a significant influence of the response, which is considered a bias, since only 6 eyes were non-responders and almost all of them had received previous PDT treatment, whereas a high number of eyes with completely dry results never underwent any PDT treatment.

So far, there is no standard treatment protocol with focus on monotherapy or combination of both anti-VEGF and PDT for treatment of PNV.

Even though 40% of our study population had a history of PDT treatment, in most cases, PDT was performed long before the development of PNV (mean 37.3±29.7 months). Only five eyes received an adjunctive PDT treatment to the anti-VEGF treatment, and three of these five (60%) achieved a completely dry status. Overall, almost all of the eyes in our study who did not have any PDT treatment still reached a completely dry status under anti-VEGF treatment (95.8%, n=23/24), showing that a good treatment outcome can also be reached without prior PDT. Nevertheless, the high recurrence rate remains an issue. There is a wide range of reported recurrence rate after successful treatment of PNV. Several studies report a positive effect of PDT treatment on recurrence rate and a possible preventive role.[11,13,15,16,29] Due to the low number of non-responders in our study, no representative results of the possible positive influence of PDT on treatment response and on recurrence of MNV activity could be shown.

In order to determine which is the best and most effective treatment regimen for PNV we need a better understanding of the pathogenesis of formation of neovascularization membranes and subretinal fluid accumulation. So far, the pathogenesis is only partly understood. There are hypotheses, that the neovascularizations in long lasting CSC occur mostly due to arteriogenesis and less or not at all due to angiogenesis process,[23,31] and that the success of anti-VEGF treatment could be explained by causing a reduction of the choroidal vascular permeability followed by reduction of the CT and absorption of SRF;[10] or that the presence of SRF might not always be a sign of MNV activity.[23] Recent studies suggest an involvement of thickened sclera in the pathogenesis of CCS and PNV,[32,33] indicating a thickened sclera in

more complex CCS[34] and even only a partial response to PDT treatment.[35] The role of scleral thickness particularly in PNV patients and their treatment response is yet to be better understood.

Limitations of this study include the limited sample size, the retrospective study design and lack of data to examine the role of concomitant PDT treatment. The question regarding the ideal treatment regimen for PNV remains unanswered. No comparison could be made between different anti-VEGF agents due to the low number of patients and the switch of medication over time. Also, due to the limited sample size, the statistical power of the study may be insufficient to detect small to moderate effects. Further prospective studies are needed to address this. Nevertheless, this study provides additional evidence on treatment regimens for a positive outcome for patients with PNV after a long-lasting anti-VEGF treatment.

Conclusions

Most PNV eyes exhibited favorable anatomical and functional improvements with anti-VEGF therapy. However, the elevated recurrence rate underscores the necessity for continuous treatment. Future studies should focus on devising approaches to reduce recurrence and improve long-term patient outcomes.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

All methods were carried out in accordance with the tenets of the Declaration of Helsinki and ethics committee of University of Cologne. This study does not include any experimental protocols. According to the local ethics committee, informed consent and extra approval is not required for retrospective analyses. All patient information is confidential and pseudonymized.

Consent for Publication

This study involved retrospective analysis of pseudonymized patient data. According to the requirements of the local ethics committee, formal informed consent was not necessary for the retrospective use of such data (s. above). However, as part of standard institutional procedures, patients had previously provided general informed consent allowing the use of their pseudonymized medical data for research and publication purposes. This consent was obtained independently of this specific study.

Acknowledgments

Preliminary results of this work have been presented as an abstract at the 2024 ARVO Annual Meeting, held in Seattle, WA, May 5–9, 2024.[36]

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Prof. Dr. Tim Krohne reports personal fees from AbbVie, personal fees from Alimera, personal fees from Astellas, personal fees from Bayer, personal fees from Novartis, personal fees from Roche, personal fees from Stada, outside the submitted work. The authors declare that they have no other conflict of interest.

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