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The Impact of the Vitreomacular Interface in Neovascular Age-Related Macular Degeneration in a Treat-and-Extend Regimen with Exit Strategy

Marion R. Munk, MD, PhD,[1,2] *Petra Arendt, MD,*[1] *Siqing Yu, MD,*[1] *Lala Ceklic, MD,*[2] *Wolfgang Huf, MD,*[3] *Andreas Ebneter, MD, PhD,*[1] *Sebastian Wolf, MD, PhD,*[1,2] *Martin S. Zinkernagel, MD, PhD*[1,2]

Purpose: To evaluate the impact of the vitreomacular interface (VMI) in a treat-and-extend (TREX) regimen with exit strategy in patients with neovascular age-related macular degeneration (nAMD).

Design: Retrospective cohort study.

Participants: Five hundred ninety-three eyes of 498 patients with nAMD.

Methods: Eyes were treated according to a TREX regimen with an exit criterion, which was defined as no signs of disease activity during 3 consecutive 16-week injection visits. The impact of the VMI and the presence of an epiretinal membrane (ERM) assessed by spectral-domain OCT were evaluated based on the parameters mentioned below.

Main Outcome Measures: Effect of vitreomacular adhesion (VMA) and ERM on mean treatment interval, number of injections, likelihood of fulfilling the exit criterion, choroidal neovascularization recurrences, CRT decrease, and BCVA improvement.

Results: During the TREX period, posterior vitreous detachment (PVD) eyes needed significantly fewer injections (mean, 10.6 ± 5.9) than VMA eyes (mean, 12.6 ± 6.7; $P = 0.0008$), and the mean injection interval was shorter in VMA eyes (8.3 ± 3.1 weeks) than in PVD eyes (9.5 ± 3.5 weeks; $P = 0.0008$). Eyes with PVD at baseline and without an ERM were 9.2 and 11.4 times more likely to fulfill the exit criterion than eyes with VMA and ERM, respectively ($P = 0.006$ and $P = 0.004$, respectively, corrected). Although CRT decrease ($P = 0.16$) and BCVA improvement ($P = 0.32$) did not differ with respect to the VMI configuration, ERM had a significant impact on CRT decrease (ERM present, +11 ± 198 μm vs. ERM absent, −92 ± 136 μm; $P = 0.041$). Vitreomacular adhesion at treatment cessation was associated significantly with disease recurrence (likelihood ratio, 7.8; $P = 0.013$, corrected), whereas the presence of an ERM was not associated with choroidal neovascularization recurrence ($P = 0.18$).

Conclusions: The configuration of the VMI and the presence of an ERM have a significant impact on the treatment frequency, the chance to meet the exit criterion in this TREX regimen, and the recurrence risk after treatment cessation. This indicates that eyes with VMA should be monitored carefully for new disease activity after treatment cessation. *Ophthalmology Retina 2017;■:1–7 © 2017 by the American Academy of Ophthalmology*

Disease progression in neovascular age-related macular degeneration (nAMD) can be retarded successfully with anti–vascular endothelial growth factor (VEGF) agents.[1,2] Different treatment regimens currently can be applied successfully, and several trials have demonstrated that the administration of fixed, as-needed (pro re nata [PRN]), capped PRN, or treat-and-extend (TREX) protocols with intravitreal anti-VEGF injections leads to good visual outcomes, although real-life results fall somewhat short of the treatment success obtained in clinical trials.[1,3–7] At present, TREX protocols in particular are exploited frequently to optimize the risk-to-benefit ratio, to maximize the cost-effectiveness, and to reduce the treatment burden and the number of visits.[8] In such protocols, monthly injections are given until clinical remission is achieved, followed by gradual extension of the treatment intervals during disease stability. Although guidelines for managing interval extension and rescue in case of relapse are well established, little is known about suitable approaches for treatment cessation after maximum interval extension and whether phenotypic markers for disease recurrence exist.[8]

Individual treatment efficacy, treatment need, and response differ significantly among patients suffering from nAMD, regardless of treatment regimen.[9–12] Several predictors for individual treatment need, response, and potential visual function outcome have been identified, including choroidal neovascularization (CNV) lesion size, baseline visual acuity, age, and the presence of intraretinal cysts or

http://dx.doi.org/10.1016/j.oret.2017.07.010
ISSN 2468-6530/17

pigment epithelial detachment.[12–15] One of the determining factors that seems to alter treatment frequency and visual function improvement is the status of the vitreomacular interface (VMI).[16–20] Beside the fact that vitreomacular adhesion (VMA) seems to be associated with development of nAMD,[21,22] the presence of VMA was reported to induce less favorable outcomes in nAMD patients treated with intravitreal anti-VEGF.[18,19] Subsequent studies also identified diverging treatment needs in eyes with posterior vitreous detachment (PVD) and eyes with VMA.[16,17] Although eyes with PVD showed comparable treatment results when treated quarterly versus monthly, eyes with VMA revealed favorable visual outcome when treated monthly, with superior visual function gain compared with the quarterly treated group.[16]

Although several studies have been conducted to describe the potential impact of the VMI on treatment efficacy in nAMD, little is known about the impact of the VMI in TREX regimens, and hardly anything is known about the potential effects on disease recurrence or the likelihood to reach exit criteria. To address this knowledge gap, this study evaluated the potential influence of the VMI in a TREX regimen with a predefined exit strategy and its impact on disease recurrence after treatment cessation in patients with nAMD.

Methods

This retrospective study identified in the institutional database patients with nAMD receiving intravitreal injections, per a TREX regimen, with ranibizumab or aflibercept at the Department of Ophthalmology, Inselspital, Bern University Hospital. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Bern Institutional Review Board committee (KEK no. 093/13). To screen for previous studies evaluating the impact of the VMI in a TREX regimen, we performed a PubMed search including the keywords *treat and extend*, *VMI*, *vitreomacular adhesion*, *posterior vitreous detachment*, *neovascular age-related macular degeneration*, *wet AMD*, and *exudative AMD*.

Inclusion criteria comprised the treatment with ranibizumab or aflibercept according to our TREX protocol between January 1, 2014, and December 31, 2015. Patients previously treated with photodynamic therapy or laser photocoagulation were excluded. Patients were excluded from the evaluation of the mean treatment interval if there was a discrepancy of the treatment interval of more than 2 weeks between the scheduled and the effective visit. A switch from ranibizumab to aflibercept or vice versa during the study period was an exclusion criterion as well.

Treatment Regimen

Until 2013, patients were treated with a ranibizumab loading dose followed by a capped PRN regimen with monthly visits and mandatory quarterly injections.[7] Since 2014, all patients have been treated according to the Bern TREX regimen using either aflibercept or ranibizumab.[8,23] Briefly, the Bern TREX protocol includes best-corrected visual acuity (BCVA) testing using the Early Treatment Diabetic Retinopathy Study charts and Spectralis spectral-domain (SD) OCT (Heidelberg Engineering, Heidelberg, Germany) examination at each visit, followed by an intravitreal injection with either aflibercept or ranibizumab. The second injection is performed 4 weeks after treatment initiation. Thereafter, the treatment interval is adjusted based on the SD OCT findings and Early Treatment Diabetic Retinopathy Study visual acuity. In the case of stability, the treatment interval is extended by 2 weeks. Stability is defined as the absence of intraretinal fluid, subretinal fluid, and sub–retinal pigment epithelium fluid on OCT. Disease was classified as stable if there was persistent subretinal fluid below the fovea of less than 50 μm, but no change in subretinal and sub–retinal pigment epithelium fluid and stable visual acuity (±5 Early Treatment Diabetic Retinopathy Study letters compared with the last 3 visits) at the third consecutive examination. In cases of relapsing activity during the extension period, the interval was shortened consecutively by 1 week until stability was reached again. This treatment interval then was maintained for the next 6 months. After these 6 months, the intervals could be extended again. The minimum interval was 4 weeks, and the maximum interval was 16 weeks. If stability was noted at 3 consecutive 16-week injection visits, the exit criterion was met and treatment ceased. After cessation, the patient was examined in the retina clinic on a regular basis every 3 to 4 months without receiving injections (Fig 1).

Study Variables and Evaluation

Medical records were reviewed for demographic data, absolute numbers of intravitreal injections since treatment initiation, as well as the number of injections starting in January 2014, when all were treated according to a TREX protocol. Furthermore, absolute treatment duration, TREX treatment duration, and the mean treatment interval in the TREX protocol were assessed. Eyes reaching the exit criterion until August 31, 2016, were assessed in more detail, paying special attention to central retinal thickness (CRT) and BCVA at treatment initiation and cessation. These patients also were evaluated for disease recurrence until October 2016.

Spectral-domain OCT scans (6 × 6-mm volume scans including 49 scans with 16 images averaged and 1 vertical and horizontal central line scan each of 9 mm and 25 images averaged) were examined for the configuration of the VMI. Spectral-domain OCT scans were analyzed at treatment initiation and at the last

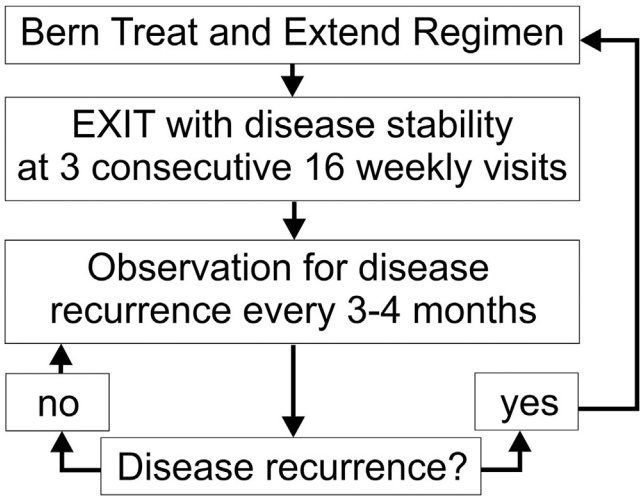

Figure 1. Diagram showing the exit strategy in the Bern treat-and-extend (TREX) regimen. As soon as stability—defined as absence of intraretinal, subretinal, and sub–retinal pigment epithelium fluid on OCT for 3 consecutive 16-week visits—is achieved, the exit criterion is fulfilled and treatment can cease. The eye then is observed on a regular basis every 3 to 4 months without receiving injections. The TREX regimen is started again with disease recurrence.