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Aflibercept for Patients with Neovascular Age-Related Macular Degeneration in Routine Clinical Practice in Germany

Twelve-Month Outcomes of PERSEUS

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Purpose: To explore real-world effectiveness of intravitreal aflibercept injection (IAI) for neovascular age-related macular degeneration (nAMD) in Germany.

Design: A 24-month, prospective, noninterventional, noncontrolled, multicenter observational cohort study.

Participants: Patients (n = 848) with nAMD treated with IAI.

Methods: Patients (n = 988) were screened at 67 study sites. Therapeutic decisions were made by the treating physician. Primary end point analysis was performed after 12 months for the entire study cohort and for predetermined subgroups of treatment-naïve and previously treated patients. Additionally, outcomes with regular injection intervals (bimonthly after 3 monthly injections) were compared with those of patients with irregularities in their treatment regimen.

Main Outcome Measures: The primary end point was the mean change in visual acuity (VA) from baseline after 12 months. Other key end points included the proportions of patients gaining 15 letters or more and patients with reading vision (≥70 letters). Furthermore, the number of injections, anatomic measurements, and safety data were recorded.

Results: Mean ± standard deviation VA improvement was 5.3±17.4 letters in treatment-naïve patients and −0.1±15.6 letters in previously treated patients ($P \leq 0.0001$), and that of the total study group was 2.9±16.8 letters. Baseline VA was 53.4±17.9 letters for treatment-naïve patients, 52.9±18.4 letters for previously treated patients, and 53.2±18.1 letters for the total patient population. Treatment pattern was associated with VA outcome: best outcomes—an average VA gain of 8.0±17.7 letters—were seen in treatment-naïve patients in the regularly treated population, whereas irregularly treated, treatment-naïve patients achieved a mean VA gain of only 4.0±17.1 letters. Among previously treated patients, regular treatment also was associated with better outcomes (+3.1±10.7 vs. −1.1±16.8 letters). For the total study group, the mean VA gain was the following: regularly treated population, 6.1±15.6 letters; irregularly treated population, 1.5±17.1 letters ($P = 0.008$). No cases of endophthalmitis were observed during the first 12 months of the study. Adverse events were in line with the known safety profile of IAI.

Conclusions: After 12 months of treatment with IAI, treatment-naïve patients showed substantial functional benefit, whereas previously treated patients maintained their VA. With regular IAI treatment, it seems that similar results as those in pivotal IAI studies can be achieved in routine clinical practice. *Ophthalmology Retina 2017;■:1–11 © 2017 Published by Elsevier Inc. on behalf of the American Academy of Ophthalmology*

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Age-related macular degeneration is a chronic, progressive disease and a leading cause of legal blindness in industrialized countries.[1] Neovascular age-related macular degeneration (nAMD), characterized by choroidal neovascularization, is driven by vascular endothelial growth factor (VEGF) overexpression.[2] The introduction of intravitreal VEGF inhibitors was a turning point in nAMD treatment and subsequently has become the standard of care.[3] Monthly intravitreal injections, as evaluated during phase 3 clinical trials, are associated with improvements in visual and anatomic outcomes. However, the high frequency could be a significant treatment burden for patients, caregivers, and

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physicians. Furthermore, concerns exist that monthly treatment may lead to overdosing in a large proportion of patients. Generally, such a regimen is considered difficult to implement in clinical practice. After the pivotal trials for ranibizumab, further studies evaluated the possibility to extend treatment intervals.[4–8] To reduce management burden, individualized dosing regimens, such as pro re nata (PRN) or treat-and-extend (TREX) regimens, have been evaluated[9–12] and are endorsed by German professional ophthalmologic societies.[13] Although the introduction of VEGF inhibitors was accompanied by a significant reduction in nAMD-related legal blindness,[14] observational study data show that randomized clinical trial vision outcomes are not always consistent with routine clinical practice outcomes.[15,16]

The retrospective AURA study, as well as the prospective WAVE and COMPASS studies, assessed long-term treatment of nAMD under real-world conditions.[4,17–19] The following findings are common to those studies. First, most patients received fewer injections or monitoring visits than would be expected, based on phase 3 study results of ranibizumab. Second, although visual acuity (VA) improved during the initial treatment phase, this initial VA gain could not be upheld during the maintenance phase, and VA deteriorated to baseline levels by the end of the follow-up period. Finally, this coincides with a significantly reduced number of visits and injections after the initial months of treatment. Consequently, there remained a need for therapies that could provide functional efficacy and anatomic disease control equivalent to monthly ranibizumab, while reducing the burden of monthly injections or monthly monitoring visits.

Aflibercept (Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) is a receptor fusion protein. Intravitreal aflibercept is specifically purified and formulated for intraocular application. The binding affinity of aflibercept to VEGF is substantially greater than that of bevacizumab or ranibizumab, as shown in preclinical studies.[20,21] In patients with nAMD, bimonthly injections (after 3 initial monthly doses) were clinically equivalent to monthly injections of ranibizumab.[22] Consequently, the European Medicines Agency approved intravitreal aflibercept for the treatment of nAMD as an injection every 2 months after 3 initial monthly injections.[23] However, data on outcomes with this dosing regimen when implemented in routine clinical practice are lacking. Under real-world conditions, patients typically have a wider range of disease presentation. A considerable proportion previously were treated for nAMD, and both ocular as well as nonocular comorbidities are common. Additionally, patients may be unable to adhere to a strict appointment schedule because of such comorbidities or other scheduling conflicts. Furthermore, in Germany and other countries, there is widespread endorsement of as-needed (PRN) treatment approaches. This also may influence outcomes under real-world conditions.[3,24,25]

The Prospective Noninterventional Study to Assess the Effectiveness of Aflibercept in Routine Clinical Practice in Patients with Neovascular Age-Related Macular Degeneration (PERSEUS) aimed to explore the efficacy of intravitreal aflibercept injection (IAI) and to describe follow-up and treatment patterns for nAMD in both treatment-naïve and previously treated patients in routine clinical practice in Germany. Another important focus of this study was to assess the impact of potential deviations from the regular treatment intervals (in accordance with the European Union Summary of Product Characteristics [SPC]) on patient outcomes. In this article, we present results of the 12-month analysis.

Methods

Study Design

PERSEUS is a prospective, observational, noncontrolled, noninterventional, multicenter cohort study conducted in 66 ophthalmologic clinics and practices throughout Germany. Patients were enrolled consecutively from July 2013 through March 2015 and were followed up for 24 months. All participants provided written informed consent. Ethics approval was obtained from the respective independent ethics committees or institutional review boards. All treatment decisions, including the decision to treat with IAI, were made by the treating physician, independently of study participation. The study was performed in accordance with the tenets of the Declaration of Helsinki.

Eligibility

Neovascular AMD patients treated with IAI in accordance with the local SPC were eligible for the study. Exclusion criteria were as listed in the local SPC. In addition, patients with scarring, fibrosis, or atrophy involving the center of the fovea or who were treated for nAMD with any other agent in the study eye were excluded. Eyes with retinal pigment epithelium tears, detachment, or lesion of the retinal pigment epithelium were eligible. Previous treatment for nAMD, including treatment with anti-VEGF agents (ranibizumab, bevacizumab, pegaptanib), was permitted. A washout period (previously treated patients) before initiation of IAI treatment was not required.

Objectives

The primary end point was the mean change in VA from baseline. Visual acuity was assessed by the treating physician in accordance with his or her routine clinical practice; data then were converted to logarithm of the minimum angle of resolution (logMAR) units and Early Treatment Diabetic Retinopathy Study (ETDRS) letter score to ensure consistency as described previously (see Supplemental Table 1, available at www.ophthalmologyretina.org).[26,27] Other key outcomes include monitoring of disease activity and treatment pattern. To this end, the number of visits, injections, and ophthalmologic assessments as well as outcomes from OCT measurements (e.g., mean change in central retinal thickness and proportion of patients with no fluid) were documented. Furthermore, the mean time from indication of IAI treatment by the treating physician to start of treatment was calculated. Data were analyzed for the entire study cohort and were stratified by treatment-naïve and previously treated patients. In addition, outcomes were compared between patients treated at regular intervals (regular treatment) and patients whose injection intervals deviated from a regular treatment regimen (irregular treatment). Patients were considered to have been receiving regular treatment if they were treated in line with the local SPC,[22] allowing for real-life clinical practice flexibility, as also used in other studies of patients treated with IAI[26] (regular treatment: loading dose of 2-mg IAI once per month [−1 week or +2 weeks] for 3 months, followed by 2-mg