Aflibercept for Patients with Neovascular Age-Related Macular Degeneration in Routine Clinical Practice in Germany: Twelve-Month Outcomes of PERSEUS

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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 < 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

Supplemental material available at www.opthalmologyretina.org.

Age-related macular degeneration is a chronic, progressive disease and a leading cause of legal blindness in industrialized countries. Neovascular age-related macular degeneration (nAMD), characterized by choroidal neovascularization, is driven by vascular endothelial growth factor (VEGF) overexpression. The introduction of intravitreal VEGF inhibitors was a turning point in nAMD treatment and subsequently has become the standard of care. 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
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. To reduce management burden, individualized dosing regimens, such as pro re nata (PRN) or treat-and-extend (TREX) regimens, have been evaluated and are endorsed by German professional ophthalmologic societies. Although the introduction of VEGF inhibitors was accompanied by a significant reduction in nAMD-related legal blindness, observational study data show that randomized clinical trial vision outcomes are not always consistent with routine clinical practice outcomes.

The retrospective AURA study, as well as the prospective WAVE and COMPASS studies, assessed long-term treatment of nAMD under real-world conditions. 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. In patients with nAMD, bimonthly injections (after 3 initial monthly doses) were clinically equivalent to monthly injections of ranibizumab. Consequently, the European Medicines Agency approved intravitreal aflibercept for the treatment of nAMD as an injection every 2 months after 3 initial monthly injections. 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.

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 were then converted to logarithm of the minimum angle of resolution (logMAR) units and the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score to ensure consistency as described previously (see Supplemental Table 1, available at www.ophthalmologyretina.org). 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, allowing for real-life clinical practice flexibility, as also used in other studies of patients treated with IAI (regular treatment: loading dose of 2-mg IAI once per month [−1 week or +2 weeks] for 3 months, followed by 2-mg...
IAI every 2 months [6–12 weeks], to a total of ≥7 IAI s at 12 months). Safety data were collected as prescribed by the routine adverse event collection process.

**Statistical Analyses and Missing Value Imputation**

Statistical analyses were explorative and descriptive. All patients with at least 1 documented IAI were included in the safety set. The effectiveness set consisted of patients from the safety set with a baseline and at least 1 postbaseline VA assessment. Because of the observational nature of this study, there was no fixed visit schedule. Consequently, the timing of measurements varied more between patients than it would have in a randomized clinical trial, and the extent of collected data depended on routine clinical practice in the study centers. During treatment initiation (until month 2), a window of ±15 days was allowed for all time points; for the subsequent maintenance phase, this window was broadened to ±30 days. Therefore, the number of included patients may vary for different end points. Changes from baseline in VA and central retinal thickness were analyzed for time points equivalent to months 1 and 2, as well as months 4, 6, 8, 10, and 12. The last observation carried forward (LOCF) approach was used to impute missing values after the first 120 days after the first injection. A supportive analysis included the last observed measurement in the analysis intervals without imputation of missing values. The Wilcoxon rank-sum test was used to compare changes in VA between patient groups. To investigate the association between selected covariates and change in VA letter score between baseline and follow-up after 12 months, linear regression was performed. First, univariate linear regression was performed for the dependent variable change in VA letter score after 12 months. Afterward, all independent covariates (baseline VA letter score, age at indication, gender, and baseline central retinal thickness [CRT], baseline lesion characteristics measured by fluorescein angiography [FA], and pretreatment and regular or irregular treatment defined by deviations from the treatment scheme as specified in the SPC) were entered into a stepwise multivariate linear regression. The entry level was \( P = 0.5 \) and the stay level was \( P = 0.05 \). All remaining significant covariates were considered to be associated with the change in VA letter score after 12 months. To avoid different sample sizes, missing observations were dropped for univariate and multivariate regression, respectively. In further analyses, logistic regression was used to investigate the association between baseline covariates and regular or irregular treatment. To determine the association, univariate logistic regression was performed for the dependent variable regular or irregular treatment with the outcomes of regular and irregular. Afterward, all independent covariates (baseline VA letter score, age at indication, gender, baseline CRT, lesion type on FA, and previous treatment) were entered into a stepwise multivariate logistic regression for the above-mentioned dependent variable. The entry level was \( P = 0.5 \) and the stay level was \( P = 0.05 \). Safety was assessed on the safety set, which included all patients who received at least 1 IAI treatment.

**Results**

**Patient Disposition and Baseline Characteristics**

Between July 2013 and March 2015, PERSEUS enrolled 848 patients in 66 study sites throughout Germany. With 46 medical practices, 12 municipal hospitals, and 8 university hospitals, the distribution of study sites closely reflects medical care in Germany. Eight hundred forty-eight patients were included in the safety set analysis. Forty-six patients from the safety set were excluded from data analysis because of a missing VA assessment at baseline or no documented follow-up visit. Consequently, the effectiveness set contained 802 patients (see Supplemental Fig 1, available at www.opthamologyretina.org). During the first 12 months of the treatment period, 223 patients (26.3% of the safety set) discontinued the study. For 59 patients (7.0% of the safety set) who discontinued the study during the first year, reasons for drop-out were not specified by the treating physician. Subsequent inquiries revealed that 15 of those patients dropped out of their own accord. In another 15 patients, lack of disease activity was cited as the cause for discontinuation. The remaining causes are currently being investigated.

The most frequently specified reason for discontinuation was treatment switch (5.4%). Treatment switch was not necessarily induced for medical reasons and occurred in both groups of patients to a similar extent. Notably, more than half of the 46 patients who switched treatment had either a stable VA (10 patients) or even an improvement of VA (16 patients) at last measurement after baseline and before discontinuation of IAI. Only 16 patients who underwent treatment switch had experienced loss of vision compared with baseline. Of those, only 2 had been treated regularly before switching was initiated.

Among all patients, 2.5% were lost to follow-up, 2.2% changed their treating physician, and 1.3% withdrew consent. Eight patients (0.9%) discontinued treatment because of adverse events, and 4 patients (0.5%) died. Only 4 patients dropped out because of lack of efficacy, physician’s decision, or disease recurrence. For 43 patients (5.1%) who permanently discontinued treatment, a variety of individual reasons were assigned, such as cost or reimbursement, no disease activity, or patient demand.

**Table 1** summarizes demographic and medical background data. Mean age of the effectiveness set was 77.7±7.8 years, and 61.6% were women. Mean baseline VA was similar in treatment-naïve and previously treated patients with available change after 12 months (53.4±17.9 letters and 52.9±18.4 letters, respectively).

**Previous Treatment and Treatment Patterns**

Almost half of the study cohort (44.3%) previously had been treated with other drugs for nAMD. Most of those patients (69.9%) had received ranibizumab exclusively, 20.0% had been treated with off-label bevacizumab, and 6.5% had been treated with both ranibizumab and bevacizumab. Less than 5% had been treated with other agents or methods. The average duration of previous treatment was 15.5±16.9 months. During this period, patients received a mean of 6.6±6.0 ranibizumab injections and 2.1±5.0 bevacizumab injections. The time between the last injection of the prior treatment and the initial IAI was 90 days or fewer for 33.1%, 90 to 180 days for 24.2%, and more than 180 days for 35.5% of the patients who had received ranibizumab only. For off-label bevacizumab treatment only, the intervals were 90 days or fewer for 50.7%, 90 to 180 days for 15.5%, and more than 180 days for 25.4% of the patients. The interval was not evaluable for 7.3% and 8.5% of patients who received ranibizumab or bevacizumab only, respectively.

**Table 2** summarizes treatment patterns in both treatment-naïve and previously treated patients. Deviations from a regular treatment schedule were observed in close to three quarters of the patient population. The mean number of injections during 12 months was significantly lower in irregularly treated patients (5.2 vs. 7.5 injections in the regularly treated population; \( P < 0.0001 \), total group, 5.8 injections). Over the first year of treatment, 68.3% received fewer than 7 injections. However, a considerable proportion of irregularly treated patients still received 7 or more injections during the first year. The numbers of patients receiving 7, 8, 9, or 10 or more injections were 85, 56, 29, and 18, respectively.
During treatment initiation, the SPC prescribes 3 monthly IAIs. In the irregularly treated population, deviations from the prescribed monthly upload were observed in 30.7% of the patients (n = 182). Although most patients received monthly injections during this phase, VA was evaluated much more rarely at months 1 through 3. Only 33.9% of patients underwent monthly VA assessments during upload. For each time point (months 1–3), the percentage of patients with VA assessment varied between 56.0% and 67.1%, whereas at month 12, 85.4% of the effectiveness set was represented. This mirrors the common practice of deferring VA assessment until after the initial treatment phase.

### Mean Change in Visual Acuity

Baseline VA for patients with available change after 12 months was 53.42±17.9 letters and 52.91±18.4 letters for treatment-naïve and previously treated patients, respectively. At month 12, treatment-naïve patients showed significantly more pronounced average improvement than previously treated patients (mean VA ± SD, 5.3±17.4 letters vs. −0.1±15.6 letters; P < 0.0001; Fig 1). The number of injections in both groups was practically identical during the first year (5.8±2.2 injections and 5.8±2.4 injections; P = 0.79).

### Table 1. Baseline Characteristics of the Effectiveness Set

<table>
<thead>
<tr>
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<th>Treatment-Naïve (n = 447)</th>
<th>Previously Treated (n = 355)</th>
<th>Total (n = 802)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), yrs</td>
<td>77.5 (7.7)</td>
<td>78.0 (8.0)</td>
<td>77.7 (7.6)</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>273 (61.1)</td>
<td>221 (62.3)</td>
<td>494 (61.6)</td>
</tr>
<tr>
<td>Baseline FA available, no. (%)</td>
<td>332 (74.3)</td>
<td>140 (39.4)</td>
<td>472 (58.9)</td>
</tr>
</tbody>
</table>

### Table 2. Key Characteristics and Outcomes of Regularly and Irregularly Treated Patient Populations (Effectiveness Set)

<table>
<thead>
<tr>
<th></th>
<th>Regularly Treated Population</th>
<th>Irregularly Treated Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (n = 802), no. (%)</td>
<td>209 (26.1)</td>
<td>593 (73.9)</td>
</tr>
<tr>
<td>Mean age (SD), yrs</td>
<td>77.9 (7.5)</td>
<td>77.7 (7.9)</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>131 (62.7)</td>
<td>363 (61.2)</td>
</tr>
<tr>
<td>Mean retinal thickness, µm</td>
<td>351.4</td>
<td>349.6</td>
</tr>
<tr>
<td>Baseline mean VA letter score (SD)*</td>
<td>53.6 (17.4)</td>
<td>53.0 (18.5)</td>
</tr>
<tr>
<td>Baseline FA available, no. (%)</td>
<td>127 (60.8)</td>
<td>345 (58.2)</td>
</tr>
<tr>
<td>Mean no. of injections at month 12 (SD)</td>
<td>7.5 (0.6)</td>
<td>5.2 (2.3)</td>
</tr>
<tr>
<td>Mean VA gain at month 12 (SD)</td>
<td>6.1 (15.6)</td>
<td>1.5 (17.1)</td>
</tr>
<tr>
<td>Treatment-naïve patients (n = 447), no. (%)</td>
<td>130 (29.1)</td>
<td>317 (70.9)</td>
</tr>
<tr>
<td>Mean age (SD), yrs</td>
<td>77.2 (7.3)</td>
<td>77.6 (7.8)</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>79 (60.8)</td>
<td>194 (61.2)</td>
</tr>
<tr>
<td>Mean retinal thickness, µm</td>
<td>362.1</td>
<td>358.9</td>
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<tr>
<td>Baseline mean VA letter score (SD)</td>
<td>52.8 (17.5)</td>
<td>53.7 (18.1)</td>
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<tr>
<td>Baseline FA available, no. (%)</td>
<td>96 (73.8)</td>
<td>236 (74.4)</td>
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<tr>
<td>Mean no. of injections at month 12 (SD)</td>
<td>7.4 (0.6)</td>
<td>5.1 (2.2)</td>
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<td>Mean VA gain at month 12 (SD)</td>
<td>8.0 (17.7)</td>
<td>4.0 (17.1)</td>
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<td>Previously treated patients (n = 355), no. (%)</td>
<td>79 (22.3)</td>
<td>276 (77.7)</td>
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<tr>
<td>Mean age (SD), yrs</td>
<td>79.0 (7.7)</td>
<td>77.8 (8.0)</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>52 (65.8)</td>
<td>169 (61.2)</td>
</tr>
<tr>
<td>Mean retinal thickness, µm</td>
<td>339.2</td>
<td>339.0</td>
</tr>
<tr>
<td>Baseline mean VA letter score (SD)</td>
<td>54.9 (17.2)</td>
<td>52.2 (18.8)</td>
</tr>
<tr>
<td>Baseline FA available, no. (%)</td>
<td>31 (39.2)</td>
<td>109 (39.5)</td>
</tr>
<tr>
<td>Mean no. of injections at month 12 (SD)</td>
<td>7.5 (0.6)</td>
<td>5.3 (2.5)</td>
</tr>
<tr>
<td>Mean VA gain at month 12 (SD)</td>
<td>3.1 (10.7)</td>
<td>−1.1 (16.8)</td>
</tr>
</tbody>
</table>

FA = fluorescein angiography; SD = standard deviation; VA = visual acuity.

*Patients with available change after 12 months.
There was an association between treatment pattern and VA outcomes. Although baseline VA scores for the regularly and the irregularly treated populations with available 12-month data were similar (53.6 ± 17.4 letters and 53.0 ± 18.5 letters, respectively), regularly treated eyes experienced a significantly more pronounced mean VA increase (6.1 ± 15.6 letters vs. 1.5 ± 17.1 letters; P = 0.008; Fig 2). After adjusting for age at indication, baseline VA letter score, lesion type on FA, gender, baseline CRT, and previous treatment, the difference at 12 months remained statistically significant. Although there was no significant difference in VA increase after the first injection, group differences became notable at month 4 after treatment initiation (7.3 ± 13.8 letters vs. +3.5 ± 14.4 letters).

Treatment-naive patients achieved best outcomes with regular treatment (VA, +8.0 ± 17.7 letters). Outcomes for irregularly treated patients without prior nAMD medication showed a trend toward inferiority, with a VA gain of 4.0 ± 17.1 letters (Fig 3A). The mean number of injections was significantly lower in irregularly treated treatment-naive patients (7.4 ± 0.6 letters vs. 5.1 ± 2.2 letters; P < 0.0001). Visual acuity improvement was lower in previously treated patients (Fig 3B). However even in this group, patients with regular injection intervals benefited from IAI treatment (3.1 ± 10.7 letters), whereas during irregular treatment, the initial improvement in VA (2.0 ± 14.6 letters at 4 months) could not be maintained until month 12 (−1.1 ± 16.8 letters; P = 0.11) and deteriorated below baseline level. Previously treated patients with regular injection intervals received a mean number of 7.5 ± 0.6 injections during the first year, compared with 5.3 ± 2.5 injections in irregularly treated patients (P < 0.0001).

Further data related to each patient who contributed to the response status are included in additional graphs (Fig 4). At 12 months, the response ratio to treatment was better for regularly treated patients. In the regularly treated cohort, 60.0% of treatment-naive patients and 46.8% of previously treated patients experienced a VA gain compared with baseline, whereas 13.6% of treatment-naive patients and 20.8% of previously treated patients experienced a VA loss (Fig 4A and B). A weaker response ratio to treatment was seen in the group who received irregular treatment. More specifically, in the irregularly treated group, the number of patients with VA gain was lower for both the treatment-naive and the previously treated patients (56.2% and 40.6%, respectively), and instead increased for patients with VA loss (27.7% and 35.9%, respectively; Fig 5C and D).
Other Visual Acuity End Points

At 12 months, 32.0% of treatment-naïve patients and 14.3% of previously treated patients experienced a gain of 15 letters or more compared with baseline when subjected to a regular treatment regimen. With irregular treatment, the proportion of patients gaining 15 letters or more was 27.7% and 15.8%, respectively (Fig 5A). Notably, among patients with irregular treatment, worsening of 15 letters or more was more than twice as common as in patients with regular treatment (14.5% vs. 6.4% in treatment-naïve patients and 17.5% vs. 7.8% in previously treated patients; Fig 5B). Although regular treatment was associated with a tendency to achieve more frequently a gain of 5 letters or more, 10 letters or more, or 15 letters or more, irregularly treated patients had significantly increased odds of sustaining losses of 5 letters or more, 10 letters or more, or 15 letters or more (Fig 5C and D). A further important patient-relevant outcome was reading vision (VA, ≥70 letters). Again, irregular treatment was associated with a lower likelihood of achieving VA of 70 letters or more at 12 months: 33.5% of the irregularly treated population versus 43.1% of the regularly treated population achieved VA of 70 letters or more (P = 0.02; Fig 5E).

Anatomic Outcomes

Over the course of the study, CRT was documented for 36.2% to 48.3% of the effectiveness set (month 12: 387 of 802 patients). Central retinal thickness decreased sharply during the initial 4 months of treatment (mean ± SD change in thickness: total, −75.9±109.7 μm; treatment-naïve, −81.5±115.6 μm; previously treated, −70.5±103.9 μm). Although this initial improvement was sustained in treatment-naïve patients throughout the first year, CRT slightly increased in previously treated patients (month 12: total, −76.1±122.9 μm; treatment-naïve, −92.0±115.7 μm; previously treated, −58.5±128.3 μm; Fig 6A). Similarly, the proportion of patients without fluid (subretinal, intraretinal, or sub–retinal pigment epithelial) on OCT increased mainly during the first 4 months of treatment and then was sustained until the end of the first year (month 12: 49.8% in treatment-naïve patients, 39.4% in previously treated patients, and 44.8% in the total study group; Fig 6B). There was no clearly identifiable trend when stratifying by regular or irregular treatment. Central retinal thickness at 12 months was as follows: regularly treated population, −78.3±113.9 μm; and irregularly treated population, −75.3±126.1 μm. The proportion of patients with no fluid at 12 months was as follows: regularly treated population, 46.0%; and irregularly treated population, 44.4%.

Other Secondary Outcomes

In the first year of IAI treatment, more postinjection safety visits and OCT examinations were performed in previously treated patients. In regularly treated patients, the total number of visits was larger because of the higher number of injections (see Supplemental Table 2, available at www.ophthalmologyretina.org).

Safety Analysis

The safety set comprised data from 848 patients. Supplemental Table 3 (available at www.ophthalmologyretina.org) summarizes the documented treatment-emergent adverse events (TEAEs).
During the first 12 months of treatment, a total of 4876 injections were administered in the study eyes and fellow eyes. No cases of endophthalmitis were reported. For 3.5% of all patients, nonocular TEAEs were reported; 8.3% experienced ocular TEAEs. Ocular TEAEs include cataract (1.9%), conjunctival hemorrhage (1.2% of all patients), and corneal erosion (0.7% of all patients). One patient experienced an arterial thromboembolic event.

**Discussion**

The PERSEUS study is the first large prospective study evaluating IAI in routine clinical practice in Germany. A large cohort (n = 848) of both treatment-naïve and previously treated patients was enrolled. With a regular treatment regimen, a VA gain of 8.0 letters was achieved for treatment-naïve patients, an outcome similar to those of the pivotal phase 3 trials.

A common feature of previous observational studies with ranibizumab was an initial improvement of VA during the upload phase that could not be upheld during the maintenance phase. The decrease in VA coincides with a decrease in consistent treatment.\(^5,15-19\) Compared with the German AURA study with ranibizumab, the mean number of injections during the first year was higher in PERSEUS (AURA, 4.3 injections; PERSEUS, 5.8 injections). In PERSEUS, VA improvements after the upload phase generally were maintained until the end of the first year, although the more consistently treated patients demonstrated greater maintenance and improvement. Thus, the outcomes of PERSEUS suggest that since completion of the AURA study in 2011, medical care of nAMD patients has improved.

Regularity of treatment seems to play a major role in achieving good VA outcomes in previously treated as well as treatment-naïve patients. In fact, treatment-naïve patients receiving regular treatment achieved results similar to those in the pivotal studies for IAI. In the 1-year outcomes of the integrated VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) studies, patients of the IAI 2qg arm (2mg intravitreal aflibercept every 2 months) gained an average of 8.4 letters.\(^22\) In PERSEUS, the regularly treated treatment-naïve patients achieved a similar VA gain of 8.0 letters. This cohort received a mean of 7.4 injections during the first year, which is comparable with the mean number of injections in the VIEW studies (7.6 injections).

Several factors seem to influence treatment outcomes. Data obtained from the irregularly treated population highlights the striking impact of regular versus irregular treatment on VA-related outcomes. At baseline, no significant group differences were observed. Therefore, it is not surprising that adjusting for baseline group differences in age at indication, baseline VA letter score, lesion type in FA, gender, baseline CRT, and previous treatment yielded

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**Figure 4.** Graphs showing the quantitative response of each patient to treatment at month 12 as expressed in a change of visual acuity (VA) letter core from baseline in (A) treatment-naïve, regularly treated patients; (B) previously treated, regularly treated patients; (C) treatment-naïve, irregularly treated patients; and (D) previously treated, irregularly treated patients. Visual acuity gains were less pronounced in pretreated patients, and irregular treatment was associated more often with loss of vision. EFF = effectiveness set.
similar, significant group differences at 12 months. A considerable proportion of treatment-naïve patients (70.9%) were treated irregularly in PERSEUS, which was reflected directly in a significantly lower number of injections during the first year (5.1 injections). Although initial VA gains were similar to those of regularly treated patients (month 1: regularly treated cohort, 4.2 letters; irregularly treated cohort, 3.4 letters), these patients ultimately did not achieve as pronounced an improvement as the regularly treated cohort (8.0 letters vs. 4.0 letters in the irregularly treated cohort). However, robustness of VA data obtained during the upload phase may be limited, because only a fraction of the study cohort underwent VA examinations during this treatment phase. Irregular treatment not only is associated with inferior VA gain, but also negatively influences other patient-relevant outcomes such as the proportion of patients achieving reading vision (≥70 letters). Irregular treatment also seems to increase the risk of vision loss. Losses of 5 letters or more, 10 letters or more, and even 15 letters or more are twice as common in irregularly treated patients, and the odds ratios significantly favor regular treatment.

Figure 5. Graphs showing the proportion of treatment-naïve and previously treated patients with a visual acuity (VA) (A) improvement of 15 letters or more or (B) worsening of 15 letters or more stratified for regular and irregular treatment. Forest plots illustrating the effect of irregular and regular treatment on the proportion of patients with (C) improvement or (D) worsening of VA. Odds ratios (OR) and 95% confidence intervals (CIs) for the total study group are shown. E, Bar graph showing the proportion of patients with vision of 70 letters or more stratified for regular and irregular treatment. A–E, Effectiveness set, last observation carried forward analysis.

Figure 6. Graphs showing (A) the change in central retinal thickness (in micrometers) and (B) the percentage of patients without subretinal, intraretinal, or sub—retinal pigment epithelium fluid over the first year of intravitreal aflibercept injection treatment. The last observation carried forward method was used to impute missing data.
There was no clearly identifiable trend when stratifying morphologic outcomes by regular or irregular treatment. However, irregularly treated patients tended to undergo more frequent OCT examinations. Therefore, it is possible that good morphologic outcomes in the irregularly treated group are overemphasized, because in a PRN setting, more frequent OCT controls tend to lead to more frequent injections.

Another important factor limiting VA outcomes in PERSEUS was previous treatment with other nAMD drugs. It is generally assumed that previously treated patients are more limited in their ability to experience functional improvement, because by the time of treatment switch, nAMD may have progressed to the point of a certain degree of irreversible structural damage. It is notable that, despite this limitation, previously treated patients could still benefit significantly if they were treated on a regular basis.

Intravitreal aflibercept injection has been approved by the European Medicines Agency for 2 monthly injections after 3 initial monthly injections. This has the potential to lower the burden of monthly injections necessary to obtain outcomes similar to phase 3 results with ranibizumab, while also providing a clearly defined treatment regimen. Particularly in nAMD, regular and consistent treatment seems to be vital, because delays in treatment may lead to or exacerbate recurrences that commonly result in irreversible damage to photoreceptors and permanent loss of VA.

In PERSEUS, irregular treatment was observed in as much as 73.9% of all patients. Because the study protocol anticipated treatment according to the SPC, reasons for irregular treatment were not captured. During most of the study period, the German professional associations exclusively recommended as-needed regimens for anti-VEGF treatment, which therefore were used widely. Although it is possible to obtain good visual outcomes with a PRN regimen under clinical trial conditions, strict monthly follow-up including monthly OCT is necessary. In PERSEUS, we assumed that the patients in the irregular group were treated mainly according to the PRN regimen; however, the mean number of OCT examinations in this group was low (4.3 examinations) and did not reflect the recommendations of the German professional associations (monthly OCT controls for at least 6 months after treatment initiation).

The concern with a regular and continuous treatment approach as recommended in the IAI prescribing information is that it may result in overtreatment or undertreatment, because the actual disease activity of an individual patient may require more frequent or less frequent IAI treatments. Another approach to nAMD treatment is more individualized TREX regimens that also have been recommended by the German professional societies since November 2014. The TREX approach continues treatment regardless of CNV activity, while increasing treatment intervals. Intervals between injections are extended gradually until the longest possible treatment interval before recurrence is achieved, thus minimizing the risk of recurrences.

An Australian study, for example, has reported good VA outcomes with a TREX scheme in routine clinical practice. Both regular dosing and TREX dosing aim to suppress CNV activity continuously, thus retaining VA. In contrast, PRN regimens require recurrence of CNV activity before further treatment is possible. Another issue with PRN regimen in routine clinical practice is that it is not standardized, but rather very much depends on the experience of the treating physician. A recently published real-world study from the United Kingdom describes a significantly higher VA gain with aflibercept in continuous (fixed or TREX) treatment schemes compared with ranibizumab in a PRN scheme. A number of other observational studies suggest that in a chronic recurrent degenerative disease such as nAMD, an irregular treatment schedule consequently leads to undertreatment. Hence, the risk of undertreatment and consequent irretrievable loss of vision with PRN schemes seems higher than the risk of overtreatment with regular regimens.

The strengths of PERSEUS include the large sample size and its prospective multicenter design. Patients were enrolled in university hospitals, municipal hospitals, and clinical practices throughout Germany. The fact that they were distributed over all the different types of healthcare facilities and throughout Germany allows us to assume that the results are representative of the medical care situation in Germany. The presence of both irregularly and regularly treated populations allowed us to assess directly the impact of irregular treatment on VA outcomes in both treatment-naïve and previously treated patients.

Limitations of this study are mainly the result of its observational and uncontrolled nature. Visual acuity was assessed by each treating physician in accordance with his or her common practice, which may confound outcomes to some extent. Although baseline characteristics of the regular and irregular populations do not show relevant differences, there is some uncertainty concerning angiographic evaluation of the previously treated group: approximately 3 out of 5 of those patients did not report angiographic evaluation at baseline. Furthermore, because the non-interventional study design prohibited a predefined visit schedule, different patient populations contributed to the observed VA data at each time point. During treatment initiation, patients rarely were assessed monthly, and the depicted populations are not necessarily representative for their respective cohorts. Last observation carried forward analysis was used to assess VA changes after treatment initiation and to limit the impact of different sub-populations. On IAI discontinuation, no further data were collected. This theoretically could introduce a bias if a significant number of patients leave the study because of lack of efficacy. It may be reasonably assumed that physicians and patients who are dissatisfied with treatment efficacy possibly discontinue study participation to switch to another drug. However, among the 46 patients who underwent therapeutic switch, a clear medical rationale supporting such switching could not always be identified: only 16 patients who underwent switching had experienced loss of vision compared with baseline. Of those, only 2 had been treated regularly before switching was initiated. Most patients switching therapy had either stable (n = 11) or even improved (n = 16) vision. Thus, lack of efficacy does not seem to be a primary reason for study discontinuation.
In conclusion, PERSEUS demonstrated that during the initial year of treatment, a regular IAI treatment regimen is feasible and effective in routine clinical practice in Germany. It underlines the necessity for consistent and regular treatment regimens to obtain optimal outcomes as seen in pivotal studies with IAI.\textsuperscript{29,32,33} After the first year of treatment, TREX with intravitreal aflibercept has the potential to reduce the burden of nAMD management further while also maintaining the initial VA gains. Such TREX treatment regimens in nAMD are subject to ongoing research.\textsuperscript{29,32,33}

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**Footnotes and Financial Disclosures**

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Abbreviations and Acronyms:
AURA = a retrospective noninterventional study to assess the effectiveness of existing anti-vascular endothelial growth factor treatment regimens in patients with wet age-related macular degeneration; COMPASS = study to assess the efficacy of treatment with ranibizumab in patients with wet age-related macular degeneration in routine clinical care; CRT = central retinal thickness; FA = fluorescein angiography; IAI = intravitreal aflibercept injection; nAMD = neovascular age-related macular degeneration; PERSEUS = Prospective Noninterventional Study to Assess the Effectiveness of Aflibercept in Routine Clinical Practice in Patients with Neovascular Age-Related Macular Degeneration; PRN = pro re nata; SPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse event; TREX = treat-and-extend; VA = visual acuity; VEGF = vascular endothelial growth factor; VIEW = VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration; WAVE = Lucentis in Wet Age-Related Macular Degeneration: Evaluation of Visual Acuity and Quality of Life.

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